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**Langzeitergebnisse nach Nierentransplantation
bei kommerzieller Lebendspende und
Lebendspende von Verwandten oder
Lebenspartnern.**

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INTRODUCTION

Kidney transplantation had been started early (1954), where the first living donor transplantation was performed in Boston between identical twins. Since then, patients of end stage renal failure have been offered the choice of renal transplantation replacement therapy beside peritoneal and haemodialysis.

Kidney transplantation restoring continuous renal functions represents the most physiological replacement therapy for end stage renal disease. Its goal is to relieve patients from the burden of dialysis and to allow returning to productive life. As the goal of transplantation should not be to provide patient with a functioning graft for only one or two years but rather to offer a long term resolution of the renal disease [29].

Compared with long term dialysis, recipients of successful transplants enjoy a higher quality of life, which for obvious reasons is directly linked to the continued function of the graft, and regardless it `s complications, generally offers a longer life span and a better quality of life [32 and 127].

Although, organ donor shortage is remain one of the major barriers to kidney transplantation worldwide. Recent medical advances have increased the number of patients in need of transplantation to the point that the shortage of organs available for transplantation has reached alarming proportions. On the other hand the number of organ for donation has not [50].

The shortage is even more sever in developing countries, where the cadaver kidney donors and the other sources like cross or the exchange donor programs not yet established and even more the unavailability of suitable related donor or unwilling to donate. Moreover, long term dialysis treatment burden and its impact on the quality of life of the patients with chronic renal failure, all these reasons forcing these patients to seek an alternative solution by other means like buying kidneys. So, this led to the development of the issue of commerce in renal transplantation or kidney black market.

Commerce in renal transplantation, although, this type of donation is a way to increase the organs source for the patients, meanwhile, help the seller by getting compensation for his donation, it has been rejected by all charities, religions, societies and Laws and it considered to be unethical practice.

Commercial renal transplantation besides its unethical practice, it has been reported that it carries a high risk of complications for donor and recipients as well; moreover, it is still being practice in some countries.

Many authors had written on the possible complications of commercial kidney transplantation. Interestingly, we had observed too many patients exceeding two hundred had got commercial transplantation with variable number of complications, high mortality and poor long term outcome.

in this study we will discuss the long term outcome (Ten years follow up), regarding the medical, surgical, infectious complications and the patients and their grafts survival of some patients who had under went commercial renal transplantation in some of the third world countries and they had been followed in Libya (Zahra kidney center) and we compare them with those who had living related donor transplantation in another different center in Germany (Uni-klinik Düsseldorf), in the same period of time.

Finally, aiming to find a proper solution at least to overcome the problem of donor shortage, there are various forms of kidney donations like exchange living donor kidney transplantation that can reduce the large need for kidneys [87].

Organ Sources:

The organ sources for donation are either from living person (live donor) who is mostly from the patient's relatives or from dead person (cadaveric donor) with good organ function [111]. Certainly, there are multiple precautions, clinical and investigatory procedures must be done before proceeding for renal transplantation, but what is mostly worth emphasising is that the donor must be investigated fully for any cardiovascular, hypertension, peripheral vascular diseases, renal disease, systemic diseases, infectious diseases, malignancies and chronic debilitating lung diseases that can be affected by donation. The donor and the recipient should undergo multiple psychological assessments by psychologist and transplantation preparations carried out by Physician and nephrologists. As it has been mentioned earlier, kidney transplantation is not a new procedure [103]. Technically, it is one of the straight forward surgical operations. The main problem is how to find the matched donor for the patient.

The main kidney sources for donation are:

1. Living Donor:

Is a widely distributed practice and form a round the third of the total kidney donations. It comes from either related or non related donor.

1.1. Living Related Donor (LRD):

The kidney is usually taken from the family members (father, mother, sisters and brothers). Identical twins are usually the best source, because of high degree of HLA matching.

1.2. Living Non Related Donor (LNRD):

Kidneys are now routinely transplanted from living donors who are genetically unrelated to their recipients. Like; spouse, friends, and even anonymous donors who are unknown to their recipients. Currently it provides nearly 25% of the kidneys that are transplanted from living donors [85].

This approach has had great success, with excellent long term outcomes, that are similar to those from Transplantations from haploidentical parents or siblings [24, 118 and 123]. Virtually all transplants from unrelated living donors are HLA mismatched, so the degree of HLA disparity is no longer an obstacle to proceeding with transplantation.

The success of kidney transplantation from LNRD has created an unprecedented demand for a limited supply of donor organs, this led to development of new alternatives like;

Types of living non related kidney donation:

1.2.1. Cross Over Kidney Donation; A cross over transplantation program provides a lifesaving opportunity when a donor can not give his or her kidney to his or her recipient. If another donor - recipient couple experiences the same problem, so these kidneys can be exchanged. It has been done successfully for more than 10 years in South Korea and in United States “kidney swapping” [71]. In Europe, however, crossover transplantations have been attempted in Switzerland, in Romania, and in Netherlands [61]. While in Germany, the transplantation law demands a close personal relationship between living donor and recipient [126]. This conservative European attitude is explained by concerns surrounding the ethical and psychological implications of crossover transplantation. Crossover donation between two couples is not significantly different from direct living kidney donation, where the “net gain” is the same: The donor receives nothing, and the couple gains nothing more than they would have gained through direct donation [61].

The motivation of the donor is the same; helping a friend or a family member by giving a kidney. The possibility of meeting or knowing the donor distinguishes crossover and direct donation from cadaver donation. Crossover differs from direct donation in that there is no prior emotional closeness or familiarity between donor and recipient. Although crossover transplantation cannot be defined as commercial, a transaction is involved, which could be defined as a process of exchange or barter. The donor’s kidney goes to a stranger, but not for free. It is exchanged for something valuable, namely, another organ for a loved one. There are concerns that this might lead to a monetary trade in organs.

1.2.2. Exchange Kidney Donation; An exchange donor program was provided to alleviate the organ shortage for the patients who do not have proper living related donor due to blood type incompatibility or to lymphocyte cross-match positively. It was launched in Korea 1991 [87]. The patient and kidney survivals, following the transplantations were similar to those from living related donors [42].

The psychological benefit is a feature of exchange living donor kidney transplantation. And in order to avoid possible interfamilial conflicts, it is essential to explain the entire procedure and expected results before the operation [87].

1.2.3. Directed Kidney Donation; A directed organ donor has an established relationship or familiarity with an identified transplant recipient. The directed donor could be a genetically related family member i.e. sibling, parent, or a genetically unrelated individual (i.e. spouse, friend, acquaintance, or another person who has an emotional bond or rapport with the recipient). In rare instances, a directed donor may know of a particular recipient in need of a donated organ and only develop a relationship with that recipient for the purpose of the transplant (e.g., church members, individuals who respond to public or media notice). These donors have been accepted if they are medically and psychosocially suitable [3].

1.2.4. Non directed Kidney Donation; Another unrelated living-donor category is composed of altruistic strangers, i.e. people who offer to give a kidney to help someone they do not know. This program began in 1999 in USA, and viewed as an ethically acceptable practice where it represents 10-15% of kidney transplants are from altruistic living donors [37]. Several other transplant centres have begun to accept kidneys donated by altruistic living strangers. Many of these centres insist that such donations be non directed, meaning that the donors may not choose their recipients. On the other hand, some authors have argued that anonymous donors should be allowed to select their recipients. This had been argued by several ethicists that directed donation is unethical because it violates the principle of justice by treating people unequally. Kidney donation by altruistic strangers should be non-directed, Although there are theoretical reasons for believing that allowing directed donation would increase the number of available kidney donors, Furthermore, the strong public opposition to directed donation according to racial or religious group membership indicates that, in addition to raising concerns about inequity, allowing directed donation on this basis would likely generate widespread negative reactions that could worsen race relations; therefore, such donations should not be permitted [115].

1.2.5. Paid Kidney Donation (Commercial); Due to the gross organ demand world wide, and in the third world countries, where the cadaver kidney donors and the other sources like cross or the exchange donor programs or the availability of suitable related donor or willing to donate not present. Moreover, long-term dialysis treatment burden and its impact on the patients with chronic renal failure, forcing these peoples to seek a kidney by any other means like buying kidneys. On the other side, poverty, pay off debts, medical or other life expenses were the reasons for almost all people who sold their kidneys. This has occurred for more than a decade, in some countries (poorer countries) like; South America, South Africa, India, the Philippines, Iraq, China, Middle East, Pakistan, Russia and Turkey. In general, the circulation of kidneys follows established routes of capital from South to North, from East to West, from poorer to more affluent bodies, from black and brown bodies to white ones, and from female to male or from poor, low status men to more affluent men. Women are rarely the recipients of purchased organs anywhere in the world [107]. Although paying people to donate kidneys is a way to increase the supply of organs and help the seller, trade in organs is generally considered ethically unacceptable, so payment to living donor for their organs is illegal in almost all countries. Paid living donors, although illegal, is a routine practice in some places. On the other hand, the commercial organ trading is immoral and may decrease the number of willing related living donors [67 and 112]. However, unrelated living donor kidney transplantation will probably exist as long as cadaver organs are in short supply and will continue to offer a therapeutic alternative to chronic dialysis treatment, this problem (black markets in human organs) can be best solved by regulation rather than by prohibition [107 and 112]. The major undisputable concern about paid organ donation has been that it would lead to commercialization of organ transplantation, with an incalculable risk for exploited donor and major disadvantages for recipients unable to pay [108]. Although patients with kidney failure deserve access to optimal treatment, such treatment should not be based on the exploitation of poor people [67].

2. Cadaveric Donor:

This type of organ donation forms the major source of organs donation in the world. It forms 100% sources for heart, and 70% for liver and kidney. The donor during his or her life or/ and his or her family give permission to the health authorities to use his or her organs after death. Death here means brain death confirmed by two independent physicians.

Shortage of Organs:

Organ donor shortage is one of the major barriers to kidney transplantation worldwide. Recent medical advances have increased the number of patients in need of transplantation to the point that the shortage of organs available for transplantation has reached alarming proportions. The number of patients waiting for solid organ in recent years has increased, where the number of individuals on awaiting list currently exceeds 100,000 globally [122]. On the other hand the number of organ donors has not.

The increasing number of liver, pancreas, heart and lung transplants reflects improved medical technology, making these procedures more feasible. This advance in technology is also reflected in the increasing number of patients on dialysis for end stage renal disease. In 1995, 68,870 new renal failure patients began dialysis in the United States, with more than 214,000 currently undergoing hemodialysis or peritoneal dialysis. In 1996, 1905 dialysis patients died on the waiting list [45 and 50].

In Germany, 53,400 patients on dialysis, only 12,000 (22.4%) on the waiting list, moreover, about 3000 patients newly registered on the waiting list every year, only 2200 have been transplanted and more than 100 patients per year have been cancelled from the waiting list due to medical problems or death. on the other hand, the mean waiting time around 5 years [62].

In recent years (2004), the organ waiting list decrease for all organs except kidney. Where, there were 95,598 registered on the UNOS waiting list. 67% of them were awaiting kidney transplantation; the majority of those patients were blood group O (51%) [23].

The shortage is even more sever in developing countries, where in India less than 4000 kidney transplanted annually and the donors were non Indians [67]. Some other countries like Libya, where there is no national cadaveric program exists, furthermore, the medically suitable living related donors are often unavailable or unwilling to donate. Hence, most of the kidney transplantations are from living non related donors (bought kidneys) [63 and 64]. Although paying people to donate kidneys is a way to increase the supply of organs and help the seller, it considered to be ethically unacceptable.

Transplantation Immunology:

Human body has two defence systems, either natural or acquired. The natural immunity is the immunity that the human body born with, such as saliva, acid in the stomach, cilia in the trachea, hair in the nose, skin etc.

The acquired immunity is the immunity that the body acquires either passively or actively. Passive immunity is that immunity which is made by body immune system activation. Like; during intra uterine life and early infant life, where babies acquired IgG from their mothers through placenta, or by infusing pre prepared immunoglobulin, while the active immunisation is conducted by introducing the killed or life attenuated antigens that stimulate immune reaction, producing primary and secondary immune response.

The acquired immunity is either humoral mediate immunity or cellular mediated immunity (delayed immunity), although both reactions work together [72].

Cellular immunity is mediated by T lymphocyte through their different cell types (helper, suppressor and cytotoxic T cells). They provide help for antibody production by B cells, and they are the effectors of antigen-specific cell-mediated immunity [10, 14 and 113].

Cell mediated immunity is important in the elimination or destruction of the cells that infected with intracellular replicating pathogens such as viruses, mycobacteria, or allogenic cells (graft), or cells that differentiate abnormally as neoplasm cells.

1. T cell activation after transplantation and Pathophysiology of transplant rejection:

T cells have receptors on their outer surface (T cell receptors). These receptors recognise the protein peptides or glycoprotein antigens in the major histocompatibility molecules on the antigen presenting cells. The antigen presenting cells are dendritic cells that are the predominate class of the presenting cells [33]. Additionally, Monocytes/macrophages and

Differentiated Monocytes/macrophages can be act as antigen presenting cells. Under the influence of cytokines and chemokines, dendritic cells mature and migrate into the secondary lymphoid tissues (spleen, lymph nodes, and Peyer's patches in the intestine) where they interact with T and B cells. Antigen is taken up by macropinocytosis, in immune complexes via IgG Fc receptors, and then degraded.

During activation of the classical complement pathway by antigen-antibody complexes, this releases C4d, which is a fragment of complement component of C4. This C4d binds covalently to tissue elements (endothelial cell surface and vascular basement membrane, which is detected by immunofluorescence or immune histochemical technique at the local site of activation [80]. It considered being a durable marker of antibody-mediated injury [70]. This has a great value in diagnosis of acute rejection caused by humoral immune components and has also a significant predictor of graft survival. [54 and 80].

Recently, it has been found that CD103, which is a subset of CD8 effectors that infiltrate the graft tubular epithelium during clinical rejection episodes, predicting a causal role for CD103⁺CD8⁺ effectors in tubular injury. Accumulation of CD103⁺CD8⁺ cells within the graft, concomitant with the development of tubular atrophy and interstitial fibrosis. So, that treatment with anti-CD103 mAb dramatically attenuated CD8 infiltration into the renal tubules and tubular injury [129].

Finally, recipient body recognizes the transplanted kidney as a foreign body and treats it as it would any other foreign substance. Hence, the immune system attacks and destroys foreign transplanted kidney.

2. Pathophysiology of chronic allograft rejection or chronic graft nephropathy:

Both cellular and humoral mediated reaction in the long run after months to years, play the main role in the development of graft arteriosclerosis and chronic allograft nephropathy (CAN).

There are two known mechanisms involved in chronic allograft rejection; immunologic (antigen dependent) and non immunologic (antigen independent) mechanisms [91]. However, most cases of chronic rejection are

Caused by humoral antibodies, either directed against the major HLA or the minor antigens [81].

The production of alloantibodies against either the HLA class I or class II antigens of the donor after transplantation has been shown to be associated with chronic allograft rejection, possibly because of the activation of the indirect pathway of allorecognition.

In recent years, there has been a great deal of interest in the role of the indirect pathway of CD4⁺ T cell activation in chronic allograft rejection. Having established that donor dendritic cells made a crucial contribution to the immunogenicity of an allograft, the rejection of donor dendritic cell-depleted kidney grafts was attributed to the presentation of donor alloantigen by recipient dendritic cells [9].

Alloreactive T cells also directly recognize allo MHC molecules on the surface of donor antigen presenting cells. This response involves a high frequency of T cells and has been hypothesized to mediate predominantly acute cellular rejection. Because the number of graft derived donor APC is limited, direct priming is likely to occur only in the early period after the transplant. Nonetheless, early priming through the direct pathway will eventually result in a population of donor reactive memory T cells that can become reactivated at later time points and participate in the development of CAN. There is evidence supporting the role of directly primed T cells in CAN meaning that the recipients who experience acute cellular rejection episodes are at higher risk for CAN.

In human renal allograft recipients, pretransplantation anti HLA antibodies as detected by high panel of reactive antibody (PRA), as well as de novo post transplantation anti donor alloantibodies, can activate complement and/or macrophage mediated effector mechanisms that are thought to participate in the development of transplant vasculopathy, glomerulopathy, and interstitial scarring, in which they are the pathologic hallmarks of CAN [91].

The high degree of polymorphism in human HLA molecules and the known complexity of the human alloimmune classification suggest that each patient may have a unique immunologic and non immunologic factors influencing graft outcome.

It has been confirmed that complexity of human alloimmunity and demonstrate that direct and indirect cellular immunity as well as humoral immunity all are more prominently detectable in transplant recipients with CAN than in those with normal renal function [91].

The immunologic factors that leads to CAN including; acute vascular rejection results in immediate and extensive histological damage, they initiate chronic allograft nephropathy, and reduce graft survival. As well as, acute cellular rejection that cause minimal direct damage, unless it was severe (usually steroid resistant) or persistent sub clinical rejection.

Sub clinical rejections are common early after transplantation and are followed by chronic interstitial fibrosis, tubular atrophy, and nephron loss, contributing to chronic allograft nephropathy especially between 3 and 12 months after transplantation, and because the tubulitis in sub clinical rejection are patchy processes, the uninvolved nephrons can maintain stable serum creatinine levels by means of compensatory hyper filtration [81].

An additional factor that appears to have an important role in the development of CAN is transforming growth factor - beta 1 (TGF β 1), a profibrotic and pro inflammatory cytokine that has been implicated in the development of graft fibrosis. The levels of TGF β 1 may be increased by angiotensin II and in Cyclosporine A treated patients [62]. The presence of allograft interstitial extra cellular matrix proteins is indicators of fibrosis shown to be surrogate markers for CAN. Hence, patients receiving the Cyclosporine A based regimens were at higher risk for developing fibrosis of the kidney allograft [7].

On the other side, cytokines released during episodes of rejection, including interleukin 1, fibroblast growth factor and platelet derived growth factor play a role in promoting the fibroblast and smooth muscle proliferation in allograft vessels. So that the intimal arteritis and vessel thickening can be explained as a direct result of immunologic vascular injury.

Later on, graft atherosclerosis leads to ischemic glomerulopathy and once glomerulosclerosis occurs, the remaining glomeruli undergo compensatory hypertrophy, increased glomerular capillary hydraulic pressure, and increased glomerular filtration. These hemodynamic forces cause damage to the glomerular capillary endothelium, mesangial expansion, and accentuate the evolution of chronic transplant glomerulopathy.

The non immunological factors, such as glomerular hyper filtration, hypertension, proteinuria, hyperlipidaemia and atherosclerosis can stimulate cell proliferation that may result ultimately in the development of transplant arteriosclerosis [117].

Arteriolosclerosis and interstitial fibrosis in the allograft may also occur as a result of recurrent pyelonephritis and chronic Cyclosporine A or Tacrolimus toxicity.

The chronic damage that occurs in CAN may occur relatively early in the post transplant period.

There are several factors involved in the tissue remodeling process (collagen III, smooth muscle actin, infiltrating leukocytes, and tenascin). It has been found that levels of collagen III were elevated in the biopsies of patients who later developed CAN. Hence, measurement of these factors at early time may allow more opportunity to modify the immunosuppressant regimen to prevent further progression of the histological changes [7].

Finally, development of CAN results from an interaction between immunological and non-immunological events, this synergistic interplay might explain why it is so difficult to manage the CAN.

Immunosuppression in Kidney Transplantation:

The first successful renal transplant was performed in 1954, but it wasn't until 1960s, where Azathioprine and polyclonal anti lymphocyte preparations were employed. The introduction of Cyclosporine A (CsA) in 1984 was a major turning point in the pharmacotherapy of transplantation which markedly improved patient and graft survival. Pharmacologic factors contributing to the success of transplantation in the 1980s included management of cytomegalovirus (CMV) infection with Ganciclovir and approval of Muromonab CD3 (OKT3).

With the recent incorporation of Tacrolimus, Mycophenolate Mofetil and Cyclosporine A micro emulsion (Neoral), one year graft survival was 87% and 93% for recipients of cadaveric donor renal transplants and living donor renal transplants, respectively. Long term graft survival (greater than 1 year) has also improved since the introduction of CsA.

Classifications of immunosuppressive agents:

A. Nucleotide synthesis inhibitors;

1. Azathioprine (AZA) (Imuran); is a purine mimic antimetabolite, it has been introduced in the clinical practice in 1961. Early immunosuppression consisted of cytotoxic agents such as Azathioprine or Cyclophosphamide, which kill proliferating leukocytes after antigenic stimulation through interference with nucleic acid metabolism by reducing intracellular purine synthesis. It decreases the numbers of circulating B and T lymphocytes by inhibiting lymphocyte proliferation [30 and 73] and later reduces immunoglobulin synthesis [120]. It reduces also interleukin 2 secretion that important for lymphocyte migration and antigen recognition [8].

It also inhibits the intracellular signalling interactions downstream of the necessary co stimulatory binding by CD28 on the surface of CD4 + T cells to B7 molecules on antigen presenting cells by the produced thioguanins [20]. Both mechanisms depend upon intracellular metabolites for the antineoplastic and immune modulating effects of Azathioprine [119]. This concludes that the serum drug levels have not a significant value in treatment monitoring.

AZA is widely used in many centers for the prevention of renal allograft rejection in combination with CsA and corticosteroids. Azathioprine is usually started at a dose (2-3mg/kg/day) depending on the leucocytes count [41], and then reduced gradually to the maintenance dose of 1-2 mg/kg per day [62].

2. Mycophenolate Mofetil (MMF) (CellCept) and (Myfortic); has been introduced in the clinical practice in 1995, the recent marketed Mycophenolate Mofetil blocked the de novo pathway of purine biosynthesis and may interfere with the recruitment of lymphocytes and Monocytes to sites of inflammation. Leading to a decrease in B and T cell proliferation as well antibody production [74].

The other suggestive mechanism of action including the induction of apoptosis of activated T lymphocytes, and the inhibition of adhesion molecule expression and lymphocyte recruitment [6].

It has replaced Azathioprine as part of triple drug therapy in many centers. It has been proved that a combination of AZA or MMF, CSA and corticosteroids revealed a statistically significant reduction in the number of rejection at one year and prevention of chronic rejection as well, in the MMF treated patients.

B. Cytokine transcription inhibitors/Calcineurin inhibitors;

1. Cyclosporine A (CsA) (Sandimmun); has been introduced in the clinical practice in 1983, unlike other cytotoxic agents, CsA exerts its effect without killing effector cells, and is not effective once antigenic stimulation has occurred [50]. Cyclosporine A and Tacrolimus inhibit IL-2 elaboration by stimulated helper T cells and prevent differentiation into cytotoxic T cells. The specificity of these agents has revolutionized immunosuppressive therapy, in that they don't alter performed immunity and humoral immune system, minimizing infectious complications.

Triple therapy with Cyclosporine A (5-10mg/kg per day) [41], steroids, and Azathioprine resulted in good allograft function and fewer chronic pathological changes in allograft biopsy than seen in patients on two drugs regimen, such as steroids and Azathioprine [51].

2. Tacrolimus (Prograf); has been introduced in the clinical practice in 1994. It is more potent than CsA. It's use as an alternative to CsA in patients who have demonstrated intolerance, it is also been effective as rescue therapy in kidney transplant patients with refractory rejection [41].

C. Corticosteroids;

Prednisolone and Methylprednisolone; Corticosteroids block primary immune response through inhibition of cytokine expression, including IL-1, -2, -3, -6, tumor necrosis factor (TNF) and gamma interferon [62].

Its anti inflammatory effects include inhibition of Monocytes migrations to the area of inflammation and blockage of chemo attractant agents, permeability increasing agents and vasodilators.

Corticosteroids have been the mainstay of immunosuppression for many years, and continue to be first line of treatment of rejection and primary prophylaxis in combination with CsA, AZA or MMF.

Initial high dose steroid therapy during the first three days in renal transplanted patient [48], but usually a dose of 0.5 mg/kg body weight is given. This dose is reduced gradually to maintenance dose of 0.1 mg/kg body weight during the next six months.

In an attempt to minimize toxicity and to decrease overall immunosuppression, slow tapering and ultimate withdrawal of steroids or giving the physiological dose are considered to eliminate the corticosteroid side effects such as hypertension, adrenal dysfunction, obesity, osteoporosis, osteomalascia, hair growth in female, etc.

Recently, it is reported that steroid free immune suppressive treatment and steroid containing regime have no significant differences on the incidence of acute rejection rate, renal function stability and treating the rejection episode in the two treatment regimes, but in the contrary, the steroid free group has good blood glucose and cholesterol control [105]. Furthermore Ractliffe et al had concluded that in stable allograft function, late steroid withdrawal was feasible, and it had led to good metabolic control, but substantial proportion of patients had renal function deterioration [95].

D. T cell antibodies;

1. Lymphocyte Immune Globulin (ALG); A polyclonal antilymphocyte antibody was used in 1981 and is prepared from the plasma or serum of healthy horses hyper immunized with human thymus lymphocytes. The mechanism of action involves a reduction in the number of circulating T lymphocytes.

2. Muromonab CD3 (OKT3); Monoclonal antibodies has been used in 1986, it reduces the number of circulating T cells by specifically binding to CD3 antigen complex on mature human T lymphocytes and blocking their function.

Both of them may be used as immunosuppressive induction therapy in the first 7 to 14 days post transplant, and they appear to be equally effective for the treatment of rejection episodes that are refractory to high dose steroids.

Both polyclonal antibodies eg, anti thymocyte globulin (ATG) and the more specific monoclonal antibodies (eg, OKT3) are potent T-lymphocyte depleting agents that are extremely effective in reversing acute corticosteroid refractory rejection. These agents, however, stimulate the release of pro inflammatory cytokines, such as tumor necrosis factor (TNF), thereby substantially increasing the net state of immunosuppression and causing reactivation of herpes viruses, especially CMV and EBV.

E. New drugs;

1. Monoclonal Antibodies against IL2 receptors:

1.1. Daclizumab (Zenapax); has been used in 1998, it is a humanized monoclonal antibody [88] that block IL-2 receptor, result in inhibiting T cell activity. It has less sever side effects than conventional monoclonal antibody. It has been demonstrated that a reduction in acute rejection episodes when combined with a CsA regimen, as compared to a standard double or triple drug regimen. It has long half life that is why it is administered every other week.

1.2. Basiliximab (Simulect); a chimmeric monoclonal antibody [88] targeted against the IL-2 receptor for prevention of kidney rejection in combination with CsA.

These specific monoclonal antibodies to the IL-2 receptor, that decreases the incidences of acute rejection have also potential advantage which does not triggering cytokine release [93], and less incidence of infection and malignancy [88].

2. Anti thymocyte immunoglobulin (Thymoglobulin); has been used in 1998, it is a rabbit-derived polyclonal T cell antibody, although its similar to (ALG), it is more effective in reversing acute rejection.

3. Sirolimus (Rapamune); has been used in 1999, has demonstrated benefit in phase I and II trials in combination with CsA and corticosteroids via a reduction in acute rejection episodes. It is a macrolide antibiotic that is related to Tacrolimus, although different in its mechanism of action. It inhibits IL-2 induced binding of transcription factors. It has an antiproliferative effect that prevents the graft atherosclerosis [68]. It also has an Anti neoplastic effect that reduces the high incidence of post transplant tumors [68 and 93].

The combination of Sirolimus and CsA appears to be synergistic and may allow for a reduction or discontinuation of steroids in selected cases. It should not however, be used in conjunction with Tacrolimus. Its effect in refractory acute rejection has also been reported. Thrombocytopenia, leucopenia and elevation of cholesterol and triglycerides may be more common than that seen with CsA and may be dose related.

4. BTI 322 (Med immune); a rat derived monoclonal antibody [50] targeted to CD2 for prevention and treatment of first rejection episodes or resistant rejection [68].

5. 15-Deoxyspergualin (Gusperimus); it inhibit T cell maturation, it has been used in Japan to treat rejection, and in USA combined with Anti CD52 Ab to induce tolerance [62].

Post Transplant Complications:

The early complications of operation are either general complication like; anaesthesia complications, operation difficulties, bleeding, pneumothorax, pneumonia and atelectasia, deep vein thrombosis, pulmonary embolism and wound infection. These complications may risk the patient's life, especially if he or she is obese, old age, and male gender [27, 55, 79, and 89], or specific complications like;

A. Renal Allograft Dysfunction;

Kidney malfunctioning or failure in the early post transplantation can be due to acute rejection [66]. Although other causes of kidney failure such as obstructive uropathy, infections, dehydration, drugs misuse and disease recurrence [13, 19, 36, 43, 56, 97, 98 and 100] must be excluded.

1. Hyper Acute Rejection:

This is very rare and occurs within minutes or hours after transplantation, due to humoral mechanism i.e. anti body mediated, as a result of mismatched graft. This rejection is permanent, so that the rejected kidney should be removed and the patient returns to dialysis.

2. Acute Rejection:

Usually occurs after the patient has recovered from surgery. It is the most common form of rejection and occurs in 50 to 60 percent of cadaver donor transplants and in 10 to 15 percent of living donor transplants. Although, with improved immunosuppression early rejection has become a less common cause of transplant failure [78]. It is characterised by tissue destructions of the transplanted organ as a result of cytotoxicity of T lymphocytes infiltration, recently, humoral rejection (according to the Banff classification 97), diagnosed by either the presence of deposits of C4d in peri tubular capillaries and/or the presence of circulating donor specific antibodies [96]. The histological equivalents are the presence of neutrophils in the peri tubular capillaries and glomeruli and fibrinoid necrosis of arteries. The impact of an acute rejection on the long term outcome depends on the number of rejections, on the reversibility (complete or partial), on the time of

Onset (early or late), on the histological outlook (the Banff criteria) and on the development of humoral antibodies [92].

The contribution of rejection to post transplant mortality has decreased over time, Rajasinghe et al, reported that rejection accounted for 24 percent of deaths from 1977 to 1983, but only 9 percent of deaths from 1996 to 1999 [2]. Although in spite of this decrease, which might be due to improvements in maintenance immune suppression and/or in early diagnosis of rejection and its treatment, graft rejection remains the most important serious clinical problem after organ transplantation.

Because acute rejection has been shown to be an important predictor of chronic allograft nephropathy in most studies, it is anticipated that a lower frequency of acute rejection will translate into a decreased incidence of late allograft loss.

The newer immunosuppressive drugs, like; Tacrolimus, Mycophenolate Mofetil, Sirolimus, monoclonal antibodies against the interleukin 2 receptors, have reduced the incidence of acute rejection among recipients of renal allografts to as low as 10 to 30 percent.

The treatment of acute rejection mainly includes anti cellular and anti-humoral regimens, which based on the histological diagnosis. But in clinical practice, it was found that some acute cellular rejection, even the borderline rejection, would turn out to be of poor prognosis, although under intensive anti cellular treatment.

A first episode of acute rejection is generally treated with high dose corticosteroids. If there is no response to corticosteroids or if there are biopsy findings consistent with the occurrence of severe rejection, antilymphocyte antibody therapy is usually preferred. The administration of muromonab CD3 or T cell depleting polyclonal antibodies results in the reversal of rejection in the majority of patients. In addition, both Tacrolimus and Mycophenolate Mofetil have been shown to be effective as rescue agents in the treatment of severe or refractory rejection [41]. The combination of Tacrolimus and Mycophenolate Mofetil [41]. Has also been evaluated as a possible approach to control alloantibody production. When combined with plasmapheresis, Tacrolimus and Mycophenolate Mofetil were effective for the treatment of severe acute antibody mediated rejection

(Acute humoral rejection) [62], a condition that typically carries a 50 to 80 percent risk of graft loss. More recently, anti CD20 anti body (Rituximab) as anti B cell Ab can be useful treatment of refractory acute humoral rejection with presence of B cells infiltration [5].

3. Chronic allograft nephropathy (CAN);

formerly known as chronic rejection, the term "chronic allograft nephropathy", has been described as the progressive decline in allograft function that occurs months or years after transplantation and is not caused by acute rejection, recurrence of original disease, surgical complications, or other identifiable factors. The clinical manifestations of CAN include deterioration in kidney function (as evidenced by a slow progressive increase in serum creatinine and decline in glomerular filtration rate), proteinuria and arterial hypertension. Histologically, reveal inflammation, fibrosis, glomerulosclerosis, tubular atrophy, and vascular smooth muscle proliferation [7].

Chronic allograft nephropathy (CAN) is one of the leading causes of late renal allograft loss and represents the most prevalent reason for patients to re enter the already long waiting list for renal transplantation [91].

The number of HLA mismatches, ineffectively or untreated clinical and sub clinical rejection appears to be a risk factor for CAN that result in immediate and extensive histological damage [15].

The effects of delayed graft function appear to be particularly harmful when it is combined with acute rejection, the age of the donor, the quality of the graft, and the number of nephrons in the donor organ has been implicated as important predictors of the long term survival of the graft. Recent findings indicate that long term treatment with calcineurin inhibitors (Cyclosporine A or Tacrolimus) may also play a part in chronic allograft nephropathy. However, inadequate immunosuppression resulting from the use of insufficient doses of calcineurin inhibitors may increase the risk of chronic allograft nephropathy by means of immunologic mechanisms [88].

The natural history of chronic allograft nephropathy could be divided into two distinct phases:

- i. An early tubulointerstitial damage correlates with immunologic factors, including severe acute rejection and persistent sub clinical rejection with the addition of ischemic perfusion injury.
- ii. Later damage is characterized by progressive arteriolar hyalinosis, ischemic glomerulosclerosis, and further interstitial fibrosis associated with long term calcineurin inhibitor nephrotoxicity.

The late identification of CAN in individual patients has meant that strategies for intervening to prevent chronic renal allograft dysfunction and subsequent graft loss tend to be too little and far too late [7 and 77].

Although, there is no widely accepted therapy of the alloantigen dependent component of chronic allograft nephropathy, there have been a number of approaches to treat CAN aimed at reducing the impact of CAN, mostly centred around avoidance of calcineurin inhibitors through their elimination in all, or just selected, patients.

In the MMF “creeping creatinine” study group [7], there are some improvement of renal function has been achieved by replacing calcineurin inhibitors with Mycophenolate Mofetil in cases with CAN caused by calcineurin-inhibitor toxicity [7, 28 and 125], or with Sirolimus [17]. However, even with graft biopsy, it is not easy to exclude immunological activation in these cases of CAN. A number of patients are, therefore, exposed to the risk of late irreversible rejection after stopping the calcineurin inhibitor. It is also possible to speculate that the over expression of chemokines and cytokines and a release of antigens from the damaged kidney can favour an indirect recognition and T cell sensitization that may trigger a late rejection even in cases of CAN originally triggered by non-immunological factors [92].

Factors contributing to the development of CAN and deteriorating allograft function:

The failure of transplanted kidneys after several years of adequate function is said to be due to the development of nephrosclerosis. This complication is characterized by a progressive decline in kidney function, which is not attributable to a specific cause. Many risk factors exist for the development of chronic allograft nephropathy, including donor related factors like; donor age and black race, HLA incompatibility. The recipient related factors like; recipient age, black race, PRA value, serum creatinine at discharge and at 1 year, re transplantation, CMV, Polyoma virus infection, disease recurrence and the transplant related factors like; number of nephrons [7], as well as non immunologic factors, such as hypertension and dyslipidemia, are associated with increased risk for renal allograft damage progression [86], all could contribute to the development of CAN.

Acute rejection within the first 6 to 12 months after transplantation has been identified as one of the strongest risk factors for the development of CAN.

Calcineurin inhibitors (Cyclosporine A or Tacrolimus) may cause deterioration in renal function in a manner similar to a rejection episode and the only way to diagnose it may be by renal biopsy [91].

A reduced drug toxicity and improved control of sub clinical rejection seem to account for the majority of the improvement. This improvement in graft function at 6 months did not translate into improved long term graft survival [58].

It has become increasingly apparent that examination of graft histology can help to identify some of the specific factors operative in damaging the allograft in an individual recipient. Still, although protocol biopsies may provide some prognostic information, they are not routinely performed because the procedure carries a small, inherent morbidity, and it remains questionable as to whether therapies can be effectively altered once the detected pathologic processes are manifested in the biopsy.

Significance of Chronic Allograft Nephropathy in Kidney Transplantation:

Survival following kidney transplantation has improved steadily over the last years. However, chronic allograft nephropathy with subsequent graft loss remains a problem for two reasons;

Firstly, with the ultimate loss of the graft, patients must return to dialysis and are frequently re listed for transplantation. Indeed, this group forms a substantial portion of patients on the waiting list for kidney transplantation.

Secondly, it has been showed that mortality rates are higher in diabetic with graft failure resumed dialysis than those who had not [102].

Non immunologic factors like; hypertension, hyperlipidaemia and atherosclerosis that predict mortality among non transplant patients also may be potentially modifiable risk factors for mortality among patients with transplant failure. It has been proved that prevention, early diagnosis and treatment of co morbid conditions and the complications of chronic kidney disease may improve the survival of patients with transplant failure [40].

B. Complications secondary to immunosuppressions:

1. Infectious Complications:

Transplant recipients vulnerable to several types of infection. This is due to the immunosuppression, technical or anatomic abnormalities, environmental exposures to pathogens, and a disturbance in the patient's normal bacterial barrier. Post transplant infection seen during the first month could be; either those that were present before transplantation, or that may be exacerbated by the immunosuppressions after transplantation, or that were transmitted to the recipient with the allograft, or that would be expected in the general population undergoing similar surgery, like; wound infections, urinary tract infection, vascular access infection, and pneumonia. The last group comprises more than 90% of the infections seen in the first month after transplantation and their incidence are largely associated with technical problems [35 and 93]. The infectious complications can be classified according to its causative organism into;

1. 1. Bacterial Infections;

Occur in the early post transplant period typically involve the wound infection (90%) [62].

Urinary tract (30-60%) [62], in the first four months that can be reduced with the prophylaxis use of Trimethoprim Sulphamethoxazol.

Pulmonary infection is the most common form of tissue-invasive infection observed in transplant recipients. Hence, life threatening infections may require a reduction or discontinuation of the immunosuppression [50]. Therefore, early diagnosis and specific therapy are the cornerstones of cure.

Tuberculosis in USA (1-4%) [62], occurs especially in those who had previous history of TB infection.

Central nervous system infection in transplant recipients like; acute meningitis, sub acute or chronic meningitis is usually caused by Crypt. Neoformans, L. monocytogenes, T. gondii, N. asteroides, or metastatic Aspergillus infection and occasionally by EBV associated post transplantation lymphoproliferative disease [35].

1. 2. Viral Infections;

Viruses are among the most common causes of opportunistic infection after transplantation and it is the most important one. The risks for viral infections are either; the function of the specific virus encountered, or the intensity of immune suppression used to prevent graft rejection, or other host factors susceptibility.

Viral infection, both symptomatic and asymptomatic, causes direct effects of invasive disease and indirect effects, including immune suppression predisposing to other opportunistic infections and oncogenesis [60].

The major infections seen during the 1-6 months after transplantation are the immunomodulating viruses, such as the herpes viruses CMV, EBV, and HHV-6; HAV, HBV, and HCV; and HIV, which exert their primary direct effects during this period. More than 6 months after transplantation, patients essentially fall into 1 of 3 groups. Approximately 80% have had good transplantation outcomes. Approximately 10% have chronic viral infection, such as CMV, hepatitis, EBV, or papilloma virus, which can lead to damage of the infected organ or malignancy. The other 10% are those whose allografts are not functioning well, who have had recurrent episodes of rejection resulting in a need for greater exposure to immunosuppression and, therefore, patients with chronic viral infection are at highest risk of life-threatening infections [93].

1. 2. 1. Cytomegalovirus (CMV);

Is the most frequent viral infection in the first few months after transplant, and is associated with considerable morbidity, which causes both direct effects, including tissue injury and clinical disease, and a variety of indirect effects. Serologic tests are of great importance in defining the clinical risk from CMV at the time of transplantation (seronegative recipients of organs from seropositive donors have a greater than 50 percent risk of symptomatic disease). The diagnosis of disease due to CMV is accomplished by demonstrating viremia or tissue invasion. Currently, the best approaches to the diagnosis of CMV disease are either tests for antigenemia (CMV early antigen Pp65) [41], or quantitative polymerase chain reaction assays using blood samples or the demonstration of virus on biopsy of infected tissues [35 and 62].

The direct effects of acute CMV infection in transplant recipients usually include unexplained fever with constitutional symptoms and laboratory abnormalities, including leucopenia, thrombocytopenia, mild atypical lymphocytosis, and mild hepatitis. The indirect effects of CMV in transplant recipients are explained by the CMV mediated immune deficits that the patient is more susceptible to opportunistic infections, e.g. *P. Carinii* pneumonia or invasive Aspergillosis and the impact of CMV-induced effects on the organ transplant that participates in the development of allograft injury (dysfunction and rejection of the allograft). In addition, CMV disease has been associated with an increase in the risk of post-transplantation lymphoproliferative disorder is consistent with the effect of CMV associated cytokines, growth factors, and immune suppression.

The prevention of CMV infection is of great importance. Although there is no consensus about the optimal regimen for prophylaxis against CMV, three points are worth emphasizing [35]; First, the intensity of prophylaxis must be proportional to the intensity of immunosuppression and to the risk of viral reactivation (e.g. intravenous Ganciclovir is given during antilymphocyte-antibody therapy). Second, prophylaxis must be initiated before reactivation of the virus. Third, to prevent relapses after premature termination of prophylaxis, so the effective antiviral prophylaxis with negative surveillance studies must be maintained for at least three months [93].

The seronegative recipient of a seropositive donor or a seropositive recipient receiving augmented immunosuppression with anti lymphocyte preparations or OKT3 is at greatest risk for CMV infection. Prophylaxis with immunoglobulin preparations, like; hyper immune globulin (Cytogan), Ganciclovir i.v. and Acyclovir p.o. [50], have demonstrated efficacy in preventing CMV disease in renal transplant recipients. The Ganciclovir dose is titrated against the level of renal function [35].

1. 2. 2. Hepatitis virus:

The incidence of chronic liver disease among recipients of solid organ transplants has remained between 10% and 15% during the past 20 years. Although some of this incidence can be due to the use of certain drugs, particularly immunosuppressant. Mostly due to infection with HBV and HCV [93].

1. 2. 2. 1. HBV Infection;

A pretransplantation vaccine for patients without anti HBV antibodies has considerably lowered the transmission of HBV from transfused blood or a transplanted organ, as well as the risk of disease after transplantation. When HBV infection is acquired during transplantation, it is associated with an increased incidence of fulminant hepatitis.

It has been reported that both 10 year patient and graft survival were significantly lower among patients with either HBV or HCV infection, and the incidence of liver related mortality was significantly higher than in non infected cases [93 and 101].

A major advance in the management of HBV infection has been the introduction of Lamivudine, a nucleoside analog that appears to be safe and effective for managing HBV after renal transplantation. The drawback of Lamivudine treatment is that resistance to the drug has been observed to occur in up to 46% of renal transplant recipients within 15 months after transplantation [93].

1. 2. 2. 2. HCV Infection;

Most liver disease in kidney transplant recipients is due to HCV infection. Although HCV is not as virulent as HBV, it is more common, with prevalence 5-10 times greater in patients with end stage renal disease than in the general population, its course is more indolent than that of HBV, and its effects often are not seen for a few years after transplantation. HCV appears to have a bidirectional relationship with CMV. Researchers have observed that both clinical and sub clinical reactivation of CMV in transplant recipients were factors in HCV incidence. In addition, late onset of CMV disease has been observed in transplant recipients with recurrent HCV hepatitis but with no other CMV precipitating factors, a recent study showed coinfection with HCV and (clinical or sub clinical) CMV infection was observed to increase the incidence of HCV associated allograft failure and mortality [93].

1. 2. 3. Polyoma virus (BK) infection;

Like CMV, the Polyoma viruses (BK type) are highly prevalent in the general population; following initial infection, the viruses remain latent in the kidney becoming reactivated under conditions of impaired immune function, including immunosuppression for organ transplantation.

The prevalence of Polyoma viruses induced nephropathy among renal transplant recipients is estimated to be between 1% and 8% and the prognosis for both graft function and patient survival is poor [93].

Polyoma virus nephropathy (PVN) has been associated with premature loss of kidney function in renal transplant patients and should therefore be considered in the differential diagnosis of renal allograft dysfunction [99], a nearly 40-60% of transplant patients with PVN develop interstitial nephritis, which causes progressive graft loss [44].

There are no specific symptoms or signs. The diagnosis should be suspected in any patient with progressive graft dysfunction, particularly if treated with a combination of Tacrolimus and Mycophenolate Mofetil [92]. The presence of Decoy cells in urine which are cells that contains viral inclusions [44] may be used to monitor the patient, although the presence of decoy cells is sensitive but not very specific. Detection of virus DNA in plasma by polymerase chain reaction is more specific, renal biopsy shows interstitial nephritis with cytopathic changes and inclusion bodies.

Reduction of immunosuppression or replacement of Tacrolimus and Mycophenolate Mofetil with the use of Leflunomide [92], which is an immunosuppressive agent [50], with antiviral properties, may rescue the kidney in a number of cases [44]. Cidofovir has also been used with success [92 and 93], Vidarabine as antiviral has been used in cystitis, as well as gamma globulin has been attempted to augment the immune response [44].

1. 2. 4. Epstein Barr virus (EBV)

Like CMV, EBV infects a large proportion of the population, most often without clinical manifestation. EBV replicates easily in the Oropharyngeal epithelium and is commonly transmitted via saliva, although it can also be transmitted to a seronegative recipient from a seropositive donor. The recipient's B cells become infected while traveling through the oropharynx,

Is curtailed by a cytotoxic T cell response that accounts for the primary clinical manifestation seen in this population. In immunocompromised hosts, however, this response is impaired or absent, the lymphoproliferation occurs [93].

1. 2. 5. Human Herpes virus 6

HHV-6 is a β -herpes virus that is closely related to CMV and HHV-7. It is a potent stimulus for release of proinflammatory cytokines, which may explain its immunomodulatory and myelosuppressive effects. HHV-6 has a number of clinical sequelae; direct effects include fever, mononucleosis, interstitial pneumonitis, and hepatitis. The most recognized direct effect besides myelosuppression is encephalitis.

The coinfection between CMV and HHV-6 is common, and several studies have suggested that HHV-6 facilitates infection with CMV, as may HHV-7 as well. It is postulated that coinfection with HHV-6 and CMV promotes development of symptomatic CMV disease and that HHV-6 infection also increases the patient's susceptibility to other infections. The close association of HHV-6 and CMV is further supported by the observation that HHV-6 responds to treatment with antiviral such as Ganciclovir, although it is less sensitive to Acyclovir [93].

1. 3. Pneumocystis Carinii Pneumonia (PCP);

Is an opportunistic infection which has been virtually eliminated by the prophylactic use of Sulfamethoxazole and Trimethoprim administered as a single strength tablet daily [93]. In some centers (e.g. Düsseldorf) use it as inhalation in patients who received Zenapax as induction therapy.

1. 4. Fungal Infections;

Fungal infection, which is currently seen less frequently than viral infection, it was the primary post transplantation infection in the past. Recent advances, including reductions in the use of corticosteroids, improved surgical technique, and the development of effective treatments, have reduced the incidence of invasive fungal infection following solid organ transplantation. Although renal transplant recipients have the lowest rate of fungal infection of all solid organ transplant recipients, prolonged dialysis,

Diabetes and immunosuppression with Tacrolimus and rejection has been found to be risk factors for fungal infection among these patients. Suppression of gut flora by antibiotics, metabolic derangement favoring fungal growth (eg, use of corticosteroids), and interruption of host barriers (eg, i.v. lines or catheters) also facilitate fungal invasion [93]. As with viral infection, the risk of fungal infection is largely dependent on the interaction between exposure and the net state of immunosuppression. The most common fungal infection post transplantation is;

Candida is the most common, accounting for 90% to 95% of all invasive fungal infections in renal transplant recipients and remaining limited to the genitourinary tract in most patients. Typical manifestations include infection related to vascular access and urinary tract infection. Deep wound infection may occur in patients with diabetes. Disseminated infection occurs in less than 5% of renal transplant recipients.

Oropharyngeal moniliasis is common in the early transplant period. Hence, prophylaxis with Nystatin is routinely administered [50].

Cryptococcus Neoformans; has been reported to occur in approximately 2.8% of renal transplant recipients. This fungus has a pulmonary portal of entry; it is disseminated rapidly to the central nervous system, the skin, the bones, and soft tissue.

Aspergillus is an angioinvasive fungus, the lungs are the portal of entry. Once blood vessels are infected, tissue infarction, hemorrhage, and metastases often follow pulmonary involvement is seen in up to 90% of solid organ transplant recipients with invasive Aspergillosis. Additionally, central nervous system effects are not uncommon.

The treatment of fungal infections is with Amphotericin B and other anti fungal. Amphotericin B is associated with severe nephrotoxicity [62]. Voriconazole, a newer, broad-spectrum antifungal, has been shown to be effective in treating fungal infections that are resistant to other drugs. Interestingly, Sirolimus have strong antifungal activity, particularly against *Candida* spp. [93].

2. Malignancy:

A serious or life threatening complication of immunosuppression, in addition to infection, is malignancy this may reflect the overall degree of immunosuppression over time rather than the effect of a specific drug and its dosage. The risk of immunosuppression related malignancy is greatest in patients receiving several courses of high doses of intensive immunosuppressive therapy. Non melanotic skin and lip cancer and lymphoproliferative disease are the most common types of tumours. The incidence increasing with time after transplantation [50].

Post transplant lymphoproliferative disease manifests as a rapidly fatal B cell lymphoma developing early after transplantation. Epstein Barr virus (EBV) antibody negative patient receiving a graft from an EBV positive patient appears to be at an increased risk for lymphoproliferative diseases. The prophylaxis use of intravenous Ganciclovir in patients receiving OKT3 may reduce the incidence of EBV related lymphomas. Acyclovir, chemotherapy and reduction or cessation of immunosuppression may improve the outcome [93].

Other oncogenic viruses such as human papilloma virus associated with development of carcinomas of the cervix, vulva and perineum. HBV and HCV causing hepatocellular carcinoma are more common in the immunocompromised host.

Kaposi sarcoma, occur frequently in the early post operative course, 0.4% in western countries and 4% in Mediterranean countries [62], as a result of immunosuppressive therapy or as a result of viral infection with human herpes virus 8 (HHV-8). Anti viral against HHV-8, reduction or cessation of the immunosuppression may improve its outcome [62 and 116].

3. Cardiovascular risk:

Although transplantation confers the highest survival benefit among all the different renal replacement therapies, renal allograft recipients still have a high mortality rate compared with population controls. A European study reported on the mortality of recipients of first renal transplants to 14 times higher than the age matched population without renal failure during the first year after transplantation, and was four times higher after this period.

Cardiovascular disease is a major risk factor for morbidity and mortality in renal transplant recipients. Nearly one third of all such deaths are due to acute myocardial infarction. Diabetic patients having the worst survival post- myocardial infarction. Among those who require intervention for coronary artery disease after transplantation, myocardial revascularization is associated with acceptable survival [1]. The most common cardiovascular risks in post transplant patients are;

3. 1. Hypertension;

Occur in 60-80% [62] of transplants, it has major influence on transplant survival and mortality [124]. Acute rejections, CAN, renal artery stenosis and drugs contributes to its pathogenesis. Reduction of CSA and or steroid dose may improve blood pressure in these patients. The calcium channel blocker provides first line treatment of blood pressure. In patients with sustained elevated blood pressure, treatment with a loop diuretic is initiated. While, patients requiring additional treatment can be managed with β blocking agents or alpha blockers [50].

3. 2. Glucose Intolerance or Post transplant Diabetes Mellitus;

Post transplant DM occur in 4-20% of patients and the development of glucose intolerance is indeed much higher.

Steroids are well recognized to induce diabetes. In addition, Tacrolimus have been shown to inhibit pancreatic cell function and insulin release. Treatment with oral hypoglycaemic agents is used in those patients with moderate hyperglycaemia.

A large portion of these patients will eventually require insulin therapy. It is important to note that insulin requirements may need to be adjusted when steroid doses are reduced, and some patients may not require long term treatment. In this case diabetes education and dietary counselling are required [50].

3. 3. Hyperlipidaemia;

Is a recognized cardiovascular risk factor in renal transplant recipient, 60% of transplant patients having high cholesterol and 35% have high triglyceride [62]. CsA, Sirolimus, steroid and proteinuria are the major cause of hyperlipidaemia.

Treatment with hydroxyl methyl glutamyl Coenzyme A (HMG CoA) lower lipid in these patients and may promote renal graft survival [50 and 62].

4. Others;

Gingival hyperplasia due to CsA, treated with Metronidazol [62], osteoporosis by steroids prevented by prophylaxis with calcium and Vit. D [62] and a septic femoral head necrosis.

C. Surgical and Urological Complications:

Surgical complications following renal transplantation may have a profound negative effect on both graft and patient survival and may be minimized by careful attention to the surgical technique during organ procurement and subsequent engraftment [50]. The entire renal transplant procedure may be viewed in terms of the following components: the incision, the Reno vascular anastomosis to the iliac vessels, the ureteral re implantation and the handling of lymphatics in the renal hilum and around the iliac vessels. Surgical complications overall and urologic complications in particular, occur in only a small percentage of renal transplants [50]. The most common post transplant urological and surgical complications are;

1. Urine Leak:

Urine leak is suspected clinically when the following are present: decreased urine output, increased serum creatinine, possibly increased serum chloride, increased weight, pain and fullness over the incision and fluid drainage from the wound. It's a true emergency in the immunosuppressed transplant recipient, because urine in the wound is a strong irritant and predisposes to infection and disruption of the vascular anastomosis. Prompt diagnosis and cessation of the leak are essential. Ultrasonography is the usual test for identifying the fluid collection in the pelvis. Percutaneous fluid aspiration and demonstration of a creatinine concentration higher than serum creatinine confirms a urine leak. One cannot distinguish between urine leak and a lymphocele by visual inspection of the fluid [50].

2. Ureteral obstruction:

Develops in some cases due to oedema along the ureteral tunnel or ischemia and fibrosis of the ureter, or the spermatic cord may be a source of external ureteral obstruction, or a small kidney may rotate and produce torsion of the ureter. It is difficult to distinguish renal allograft dysfunction due to ureteral obstruction from mild hydronephrosis associated with chronic rejection, where in the late stages of chronic rejection, the renal collecting system may have poor peristalsis and demonstrate mild hydronephrosis. Progressive rise in serum creatinine not due to acute rejection and the development of hydronephrosis suggests the diagnosis.

The diagnosis is made by retrograde pyelography, a Stent placement or Balloon dilatations continue to have a role in the management of ureteral obstruction [50].

3. Lymphocele:

The lymphatic vessels surrounding the iliac vessels should be carefully tied or clipped during exposure of the vessels for anastomosis of the renal artery and vein to minimize the risk of postoperative lymphocele formation. Most lymphocele appear in the first several months post operatively this fits with the proposed aetiology. The cause of occasional late appearance of lymphocele is unclear. The signs and symptoms of a lymphocele may include; increased serum creatinine due to extrinsic compression of the ureter, oedema of the ipsilateral lower extremity or pain and fullness over the wound and lower abdomen. The diagnosis is established by the finding of a fluid collection on Ultrasonography and Percutaneous aspiration demonstrating that the fluid is lymph and not urine (i.e. fluid creatinine and potassium concentrations similar to serum). Most lymphocele recur and require definitive treatment. Laparoscopic intra peritonealization of the lymphocele has become the preferred treatment. A large window is created between the medial wall of the lymphocele and the peritoneal cavity so that further lymphatic leak is reabsorbed. Open surgery with Percutaneous closed tube drainage are also effective alternative treatments. The later procedure usually requires 3-6 weeks of tube drainage, but it may runs the risk of introducing infection, so infected lymphocele must be treated by external drainage and antibiotics. Repeated instillation of sclerosing agents like, Tetracycline [41] or Povidone has been reported as being highly effective [50].

4. Renal allograft Artery Stenosis:

It occurs in the early days post transplantation, the incidence varies between 1% and 12%. It is mainly due to technical errors include poor anastomosis, particularly in the case of end to end anastomosis of the internal iliac artery to the renal allograft artery or if atherosclerotic plaque is present in the recipient vessel. The diagnosis is considered in patient with deteriorating graft function, onset of hypertension that was previously normotensive or hypertension requires more than one therapy to be controlled. Angiography remains the gold standard for diagnosis of transplant renal artery stenosis.

Duplex ultrasound Scanning, particularly with colour flow display, which is not invasive, not toxic and easily available method for screening [124], spiral computed tomography and magnetic resonance imaging has improved the accuracy of assessment of the renal vasculature. Three options are available to manage it: conservative, angioplasty with or without Stent, or surgical correction [90].

5. Renal Artery Thrombosis:

The failure of a transplanted kidney to produce urine in the immediate postoperative period is a relatively common event. Anuria and the absence of function are caused by thrombosis of the graft artery. The causes of acute arterial thrombosis are multi factorial, like; technical errors, persistent hypotension, dehydration, pro coagulant conditions such as lupus anticoagulant and diabetes. The problem is more frequent in highly sensitized recipients, especially with positive cross match, suggesting that antibody mediated endothelial damage, despite the absence of hyper acute rejection on subsequent histological examination. An isotope perfusion scan or colour duplex scanning or graft necrosis confirmed by biopsy can confirm the diagnosis [90].

6. Renal Vein Thrombosis:

Venous thrombosis has been noted to occur in the early phase after transplantation due to external compression or torsion of the graft vein, which results in reduction of urine output and rising creatinine in a functioning graft. The clinical signs are severe pain, swelling of the leg on the side of graft anastomosis. Confirmed by a finding of non perfusion on isotope scanning or in a colour duplex examination and the ultrasound scan shows a swollen graft. Pain relieve as well as thrombolysis therapy should be initiated whenever the diagnosis made [90].

Kidney transplantation; Ethics and Laws.

Organ donation aimed to alleviate patient's illness, on the other hand, and based on the concept "do no harm" for the donor, i.e. low donor risk, the donor must be fully informed, the decision should be voluntary and independent and lastly successful recipients outcome [68].

Over the past decade, the shortage of organs for transplantation and the agonizing waiting lists for kidney transplants. This has forced many centres in the third world to the practice of commerce as organ procurement. That may have serious implications both for the patients and the society as a whole. Although, organ donation had been approved by all charities, religions, societies and Laws, as it provides a hope for those patients who suffering an end stage organ failure, provided that it should be an altruistic and free of commercialism.

Christianity has appreciated altruistic organ donation, as a sign of charity, "first of all, do not harm." Apart from organ donation with altruistic motives, commercial incentives or payment for organ donation prohibited [104].

The U.S. Conference of Catholic Bishops had permitted the transplantation of organs from living donors, but the donor must be respected [104].

The Greek Orthodox Church accepts the possibility of any kind of transplant, if it is not a commercial transaction [104].

The Church of Scotland stated that the donation must be made freely on the grounds of need, not conditionally on the grounds of creed [104].

The Jewish authorities reject out of hand the belief that payment for a kidney donation. They agree that a donation motivated by charity [104].

Kidney donations from either living or cadaveric organs are not prohibited in almost all Arabic as well as Islamic countries, the cadaver donation is not widely used except in Saudi Arabia and some other countries, nevertheless, practice of commercialism in renal transplantation was found in some centers, although it was strongly rejected. In table 1. We have summarized some of religious views that encourage the organ donation [128].

According to the venerated Hippocrates taught, "As to diseases make a habit of two things to help, or at least do no harm" [34].

The national guidelines, like, British Guidelines, DOQI Guidelines, Canadian Guidelines and European Best Practice Guidelines, generally support the use of living unrelated and living non-directed living transplantation (Evidence level B). While, commercially motivated kidney transplantation is not acceptable and all procedures must comply with existing national (regional) and EU laws. (Evidence level A) [31].

The international recommendations do not prohibit all dealings with human tissue. They are concerned with individuals or organisations gaining or offering certain types of incentive or compensation for supplying or obtaining certain types of human tissue.

According to the Convention on Human Rights and Biomedicine, it prohibits any trading transactions in all human tissue. Instead, there are differences in the type of material covered by these prohibitions and the differences in regulatory responses towards organ donors. 24 countries had conduct regulations that prohibit certain commercial dealings with human organs and these statements are summarised in Table 2 [112].

Ethics in living donor renal transplantation can be considered under four categories: (1) living related donation (2) emotionally related donation (3) altruistic donation and (4) commercialism. The ethical issues for categories 1, 2, and 3 are having been accepted, while category 4 is considered to be unethical [21].

In summery, the ethical aspects of commercial transplants were debated widely in the media as well as by the transplant community. Most professional organizations, including the Transplantation Society and World Health Organization considered these transplants to be unethical and require a solution condemning this practice.

Table 1. Some views of major religion on the organ donation.

AME (African Methodist Episcopal)	Organ and tissue donation is viewed as an act of neighbourly love and charity by these denominations. They encourage all members to support donation as a way of helping others.
Baptist	Donation is supported as an act of charity and the church leaves the decision to donate up to the individual.
Brethren	The Church of the Brethren's Annual Conference in 1993 wrote a resolution on organ and tissue donation in support and encouragement of donation. They wrote that, "We have the opportunity to help others out of love for Christ, through the donation of organs and tissues."
Buddhism	Donation is a matter of conscience.
Catholicism	Transplants are acceptable to the Vatican and donation is encouraged as an act of charity.
Christian Church (Disciples of Christ)	The Christian Church does not prohibit organ and tissue donation. They feel that it is a personal decision to be made in conjunction with family and medical personnel.
Greek Orthodox	No objection to procedures that contribute to restoration of health, but donation of the entire body for experimentation or research is not consistent with tradition.
Independent Conservative Evangelical	Generally, Evangelicals have no opposition to organ and tissue donation. Each church is autonomous and leaves the decision to donate up to the individual.
Islam	The religion of Islam strongly believes in the principle of saving human lives. The principle of priority of saving human life, it has permitted the organ transplant.
Judaism	Jews believe that if it is possible to donate an organ to save a life, it is obligatory to do so. Since restoring sight is considered life saving, this includes cornea organ transplantation.
Presbyterian	Presbyterians encourage and support donation. They respect a person's right to make decisions regarding their own body.
Protestantism	Encourage and endorse organ donation.
Seventh-Day Adventist	Donation and transplantation are strongly encouraged by Seventh-day Adventists.
Unitarian Universalist	Organ and tissue donation is widely supported by Unitarian Universalists. They view it as an act of love and selfless giving.
United Church OF Christ	The United Church of Christ supports and encourages donation.

Table 2. Regulatory prohibitions of commercial dealings in human organs: The International Digest of Health Legislation (IDHL) [112].

Australia	No federal jurisdiction, but there are prohibitions in all States. (IDHL 1991a 401)
Austria	Law of 1 June 1982 (amending the Hospitals Law of 18 Dec. 1956), s.62a (4) (IDHL 1986).
Belgium	Law No. 32 of 13 June 1986, s.4 (IDHL 1987).
Britain	Human Organ Transplants Act 1989, s.1.
Canada	No federal legislation, but there are prohibitions in commercial dealings Tissue Donation Act 1989, s.15.
Denmark	Law No. 402 of 13 June 1990, s.20 (3) (IDHL 1991b).
Finland	Law No. 101 of 2 Feb. 2001 (No. 101/ 2001) on the Medical Use of Human Organs and Tissue, ss.18 & 25(6) (IDHL 2001).
France	Law No. 94-654 of July 29 1994, Art. L. 665-13; and Decree No. 2000-409 of 11 May 2000, Articles R. 665-70-1 to R. 665-70-4 (IDHL 1994b and IDHL 2000 respectively).
Germany	Act of 5 Nov. 1997, s.17 (IDHL 1998a). (Bundesgesetzblatt, Part I, 11 November 1997, No. 74, pp. 2631-2639)' 49 IDHL
Greece	L. 2737/1999, Art. 2 (Canellopoulou-Bottis 2000, 429–430).
Hong Kong	Ordinance No. 16 of 1995, s.4 (IDHL 1995c).
India	on of Human Organs Act (Act No. 42 of 1994), s.19 (IDHL 1995a).
Ireland	No legislation. However, the Medical Council's ethical guidelines prohibit payment (Medical Council 1998, 38).
Italy	Law No. 644 of 2 Dec. 1975, ss.19 and 20 (IDHL 1977).
Japan	Law No. 104 of 16 July 1997, s.11 (IDHL 1998b).
Luxembourg	Law of 25 Nov. 1982, s.16 (IDHL 1983 and 1991a, 407).
Netherlands	Law of 24 May 1996, s.2 (IDHL 1996).
Portugal	Law No. 12 of 22 April 1993, s.5 (IDHL 1994a).
Singapore	Human Organ Transplant Act 1987, s.4 (Kurnit 1994, 42)
Slovakia	Law of 24 August 1994, ss.46 (5) and 47(3) (IDHL 1995b).
Spain	Law No. 30 of 27 Oct. 1979, s.2 (IDHL 1980a) and Crown Decree No. 426 of 22 Feb. 1980, s.5 (IDHL 1981).
Sweden	Law No. 831 of 1995, s.15 (Ministry of Health and Social Affairs 1997, Appendix 1).
Turkey	Law No. 2238 of 29 May 1997, ss.3, 4, and 15 (IDHL 1980b).
US	National Organ Transplant Act 1987, s.274(e) (federal legislation), and The Uniform Anatomical Gift Act 1987 (s.10 of which prohibits commercial dealings).



STUDY DESIGN

AIM OF THE STUDY

There are many questions came across, when we are discussing the issue of commercial kidney transplantations, like;

1. Why chronic renal failure patients seeking this kind of transplantation?
2. Has the commercial kidney transplantations; apart from it is unethically accepted, a negative impact on the recipient?
3. Dose the commercial kidney transplantations affect the long term survive of the recipient as well as the graft?
4. Are the end results of the commercial kidney transplantations comparable with the results of living related or non related donor transplantations?
5. Does patients who had commercial kidney transplantations are at increased risk of death compared to patients who have living related or emotionally motivated non related donor transplantations?

The aim of this Study is to highlights on the post transplant complications of the commercial kidney transplantation and to analyze the long term course and outcome of the patients and their grafts in those who under went commercial transplantations, and in order to answer these questions, a retrospective study was conducted to compare patients who had commercial transplantation with those who had living related transplantation in two different centers and discussing some aspects of the ethical issue.

PATIENTS AND METHODS

A total number of 368 kidney transplanted patients were examined retrospectively in the period of time between 1994 and December 2004 but in two different centres. They had been divided into two different groups:

Patients Group I (living related transplantation);

A total number of 138 emotionally motivated live donor kidney transplantations performed at the Uni-klinik Düsseldorf were the material of the study (compared group). We have looked for the followings:

Pre transplantation work up;

- Age and sex of the patients were mentioned.
- Pre transplantation data regarding donor and recipient selection and preparations were collected.
- Original kidney diseases were mentioned.
- Donor source were obtained.
- Patients were underwent an extensive medical and psychological examination before transplantation.
- Potential donors and recipients who referred to the Uni-klinik Düsseldorf for transplantation were emotionally related living donor kidney transplantation. We defined an emotionally related donor as a donor without genetic relationship (or very distant) but with a long-standing relationship and/or a strong emotional bond with the recipient.

Immunological work up;

Tissue type for class I and II antigens, blood group compatibility and a negative cross match, were considered.

Immunosuppression protocol;

Uni-klinik Düsseldorf's immunosuppressive protocols were as;

A. Triple therapy with;

- Cyclosporine A 2x 3mg/kg/day, started 3 days before the scheduled transplant operation, CsA dose was adjusted to keep the trough level between 150 and 250 ng/ml in the first 2 months and between 150 and 200 ng/ml thereafter.
- MMF 2x1 g/day started 5 days before operation.
- Methylprednisolone 500 mg i.v. during the operation and then Prednisolone started orally, then reduced successfully to reach 20 mg at three weeks, then to be further reduced by 5 mg weekly till 10mg/day at 6 months.
- In 1990s, Tacrolimus (0.5mg/kg twice daily) was introduced as rescue therapy in some cases or to replace CsA as a result of their side effects. The Tacrolimus dose was adjusted to achieve a trough level between 5 and 10 ng/ml.

B. Quadruple therapy including; mono- or polyclonal antibody treatment (ATG and OKT3) and Zenapax, Simulect in patients with four or more mismatches or patients with cytotoxic antibodies (PRA > 50%).

- Patients receiving antibody treatment were given Pneumocystis Carinii prophylaxis with Pentamidine inhalation once a week for 4 weeks then once a month for 6 months after transplantation.
- CMV prophylaxis not performed, but patients regularly screened for CMV early antigen (Pp65). In the event of conversion, early therapy for CMV infection was started.

Follow up data;

- All data was obtained from the patient's files regarding the date of transplantations, immediate and delayed medical, infectious and/or surgical complications were reported.
- Kidney function measured by serum creatinine, the date of transplantation failure was defined as the earliest time of return to chronic dialysis therapy or death with functioning graft.
- At the occurrence of clinical signs of rejection, renal biopsy was performed. Rejections were treated with Methylprednisolone pulses 250 mg/day i.v. for 5 days. Steroid resistance rejection was treated by OKT3 or ATG for 7-10 days in the event of histological signs of vascular rejection.
- In the last years and in special cases with severe vascular rejection, anti CD 20 Ab (Rituximab) and plasmapheresis had been employed.
- Cyclosporine A was substituted by Tacrolimus (Prograf) in cases of steroid-resistant interstitial rejection, or signs of Cyclosporine A toxicity in kidney biopsies. In these cases target trough levels for Tacrolimus maintained between 8-12 ng/dl.
- Presence of hypertension, before or after transplantation. Hypertension is considered when the systolic blood pressure >140 mmHg, or diastolic blood pressure >90 mmHg without treatment.
- Presence of diabetes mellitus, before or after transplantation.
- The patients who are lost to follow up (the last follow up date) were also recorded.
- Time, cause of death and death with functioning or non functioning graft was mentioned.
- Graft and patient survival rate after one, five and ten years were calculated.

Patients Group II (Commercial/bought grafts);

A total of number of 230 live non related commercial kidney transplantation performed at some of the third world country, were the material of the study (study group).

All of the patients were Libyan, who travelled on their own initiative to India, Iraq, Egypt and Pakistan where they received unrelated transplantations.

Most of them who returned after transplantation, they were admitted to Zahra centre within the first two to four weeks after operation.

Pre transplantation work up;

- The preoperative clinical findings and laboratory results were obtained from the hospital discharge papers or from medical reports that the patients brought.
- Pre transplantation data regarding donor and recipient selection and preparations, are not provided from the operating team.

Immunological work up;

Tissue type for class I and II antigens and compatibility (cytotoxicity test) were unknown for most of the patients.

Immunosuppression protocols;

The patients came with immunosuppressive protocols as;

- Cyclosporine A 12mg/kg/day, CsA trough level was between 200 and 400 ng/ml.
- Azathioprine 2-3mg/kg/day.
- Prednisolone 2mg/kg/day.

- Mycophenolate Mofetil (MMF) 2g/day had been introduced to some cases since 2000.
- Early acute rejection episodes were not clearly documented by histopathological examination and their treatment were not clearly mentioned from the transplant team, whether treated with Methylprednisolone pulses or with antibody therapy.

Follow up data;

- Follow up data were obtained for all patients regarding the Place and the date of the transplantation operations.
- Patients presented with an uneventful post-transplant clinical course and normal kidney function with stable clinical and laboratory findings were followed at the outpatient clinic, whereas those with medical and/or surgical complications were hospitalized.
- For each patient, blood biochemistry, urine analysis, creatinine clearance, electrocardiography, chest x-ray, blood Cyclosporine A level determinations by fluorescent polarization immunoassay (TDx), drainage fluid (if present) examinations, sputum and urine cultures, serological tests concerning cytomegalovirus, hepatitis B and C, were carried out. Additionally, ultrasonographic examinations of the allograft were performed as needed.
- Immunosuppressive medications that were started in the original transplant centre were kept the same. However, necessary adjustments were made in the presence of any complication.
- Intravenous Methylprednisolone with a daily dose of 500 mg for three consecutive days as administered as a first line of anti rejection therapy and then if there was no response anti lymphocyte globulin (ALG) was given with a daily dose of 20 mg/kg for 14 days.
- Medical, infectious and/or surgical complications were reported.
- Medical, and/or surgical complications were treated accordingly and supportive dialysis was performed if needed.

- Original kidney diseases were also looked for.
- Presence of hypertension, before or after transplantation. Hypertension is considered when the systolic blood pressure >140 mmHg, or diastolic blood pressure > 90 mmHg without treatment.
- Presence of diabetes mellitus, before or after transplantation.
- The date of loss of graft function after transplantation was looked for. Transplantation failure was defined as the earliest time of return to chronic dialysis or death with functioning graft.
- The patients who are lost to follow up (the last follow up date) were also recorded.
- Time, cause of death and death with functioning or non functioning graft was mentioned.
- Patient and graft survival rate after one, five and ten years were calculated.

Statistical tests:

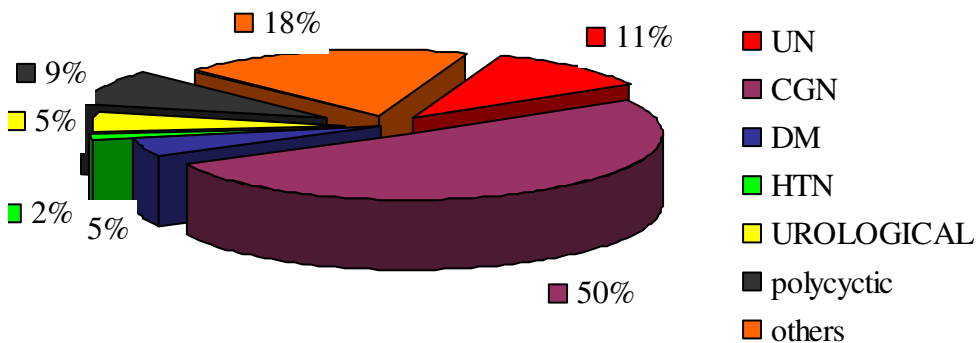
Results are expressed as mean values \pm standard deviation (SD). The Paired Student t test was used to compare the two different groups of patients and Chi square test was used to compare graft and recipient survivals in the two groups. The P value of <0.05 was considered significant. The statistical analysis were conducted by Microsoft XP excel, Minitab version 12 and SPSS (Statistical Package of Social Science) version 13 programme.

RESULTS (A)

Living related grafts - Group I (compared group);

Causes of original kidney disease;

The causes of end stage kidney disease (ESKD) were as follow;
CGN 46.3%, DM 4.3%, HTN 1.4%, unknown (UN) cause 10%, uropathy 4.3 %, poly cystic kidney 7.9% and others (17%) like; SLE, HUS, Alports syndrome, dysplasia, interstitial nephritis and nephrocalcinosis (Fig. 1).



(Fig. 1) causes of ESKD in Group I.

Patient's description;

Out of 138 patients, 78 were males and 60 were females (1.3:1), mean age \pm SD, 45 ± 13 (range 19 to 73 years).

Graft origins were as follows; 29% from parents, 32% from siblings, 26% from spouses, 3% from children, 8% from cousins [123].

Surgical complications;

Nine cases (6.5%) reported to be complicated by lymphocele formation, renal artery Stenosis occurred in 12 cases (8.7%), urinary fistula and stricture took place in only 7 cases (5%).

Medical complications;

Thirteen patients (9.5%) had developed systemic hypertension. Diabetes mellitus diagnosed in only one patient (0.9%) after transplantation.

- Ten cases (7.2%) reported to have acute rejection episodes.
- Chronic allograft nephropathy had occur in 31 (22.4%) of cases, where it was the major cause of graft failure.

Three patients (2.3%) lost their grafts and resumed dialysis as a replacement therapy.

Infectious complications;

The majority of infection during the post transplantation course was urinary tract infection, which occur in 37 cases (26%).

- Herpes zoster in 2 cases (1.4%).
- No cases of hepatitis B and C viruses have been reported.

Recipients and grafts outcome after transplantation (Fig 4):

Collectively, during 10 years follow up period after transplantation, 60 patients (43.4%) have normal followed up. 10 patients (9%) were lost follow up (Fig. 4).

Seven patients (6%) were died from which 4 patients (57%) died with functioning grafts. Out of these 7 patients, 6 patients were died during the first two year after transplantation.

The main causes of death were due to cardiovascular complications in 2 cases (28.5%) and graft failure in 2 cases (28.5%).

Patient survival rates at one, five, and ten years were 100%, 94.9% and 94.2%, respectively, (Fig. 6).

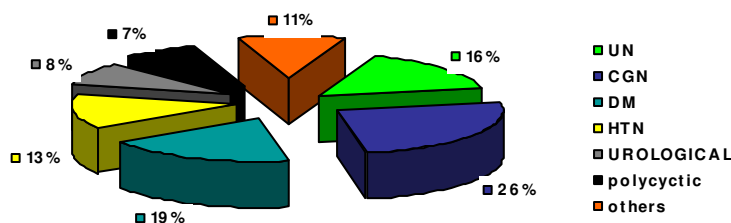
The graft survival rates at one, five, and ten years were 88.5%, 74.6%, and 71.7%, respectively, (Fig. 7).

RESULTS (B)

Commercial/bought grafts - Group II (study group);

Causes of original kidney disease;

The causes of end stage kidney disease were as follow;
CGN 24%, DM 17%, HTN 12%, unknown (UN) cause 15.5%, uropathy 5%, polycystic kidney 7% and others (10%) like; SLE, TB, pyelonephritis and tumors (Fig. 2).



(Fig.2) Causes of ESKD in Group II.

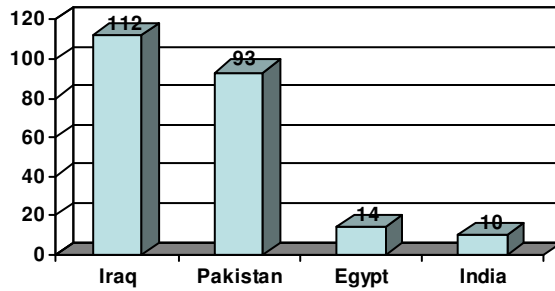
Patient's description;

The study group was 230 patients, which represents nearly half (43%) of the total number of transplanted cases, that they had been followed up at Zahra centre.

Out of the 230 patients 147 were males and 83 were females i.e. 1.7:1, the mean recipient age (Mean \pm SD) is 42 ± 12 years (range: 19 to 63 years). This means that most of the recipients were middle aged males.

Places of transplant operations;

One hundred and twelve patients (48.6%) were transplanted in Iraq, 93 (40%) in Pakistan, 14 (6%) in Egypt and 10 (4%) in India (Fig. 3).



(Fig. 3) Number of cases according to the place of transplantation.

Some of the patients were admitted with primary non- functioning grafts. At admission, the mean serum creatinine was 2.0 ± 1.6 mg/dl.

The hospital admissions at Zahra kidney center, Libya (the place of the study) took place during the first three post transplant months and were indicated for treatment of surgical and medical complications.

Surgical complications;

We found that the initial surgical complications like; wound infection in 5 cases (2%), two patients had opened wound with abscess formation, lymphocele formation seen in 20 cases (8.6%), renal artery stenosis in 2 cases (1%), and urinary fistula in 5 cases (2%). The late surgical complications as ureteral stenosis in 7 cases (3%).

Medical complications;

The medical complications were remarkable like;

- Acute rejection episodes reported in 34 cases (14.7%).
- Chronic allograft nephropathy occurred in 47 patients (20.4%), where 50 % of it had occurred in the first two years after transplantation, which was the major cause of graft failure.

Infectious complications;

The overall infectious complications were observed in 59 patients (25.6%), we summarized it as follows;

Twenty nine patients (12.6%) have HCV infection, 14 (6%) with HBV infection, 11 (4.8%) have CMV infection, 2 (1%) have Herpes zoster infection and 3 patients (1%) have got TB infection.

- Ten cases (4.3%) and 18 cases (7.8%) of the patients were serologically positive for hepatitis B only and C viruses only, respectively.
- Three cases (1.3%) had both hepatitis B and C, on the other hand 2 (0.86%) had C, B and CMV virus infections.
- Infection with hepatitis C and CMV together were diagnosed in 6 (2.6%) and only one case had both B and CMV infection.
- Urinary tract infection seen in 62 cases (27%), which was the commonest infection observed during the post transplantation course.

Chronic active hepatitis and liver cirrhosis secondary to C and B hepatitis reported in 4 patients (1.7%).

Malignancy;

Malignant diseases like; Kaposi sarcoma had occurred in 4 cases (1.7%), three to six months after transplantation.

Other medical problem related to immunosuppressions over dose like;

- Post transplant hypertension was diagnosed in 153 patients (66.5%).
- Diabetes mellitus was diagnosed in 48 Patients (2.9%).
- The occurrence of gingival hyperplasia had been seen in 10 cases (4%), the mean Cyclosporine A level in these patients were between 390 and 450 ng/dl. which had been resolved after CsA dose reduction.

Recipients and grafts outcome after transplantation (Fig.5);

- Death, as a whole occurred in 37 patients (16%), 8 patients (21.6%) died with functioning grafts, out of them 25 patients (53%) died in the first two years.

The main causes of death were; infections in 14 patients (30%), Cardiovascular complications in 9 (24%), and death due to graft failure in 9 (24%).

- Graft lost occur in 37 patients (16%) either due to graft failure or death with functioning graft, 26 patients (12.3%) resumed dialysis, out of them 5 cases (6%) resumed dialysis one year after transplantation.

- Thirty patients (13%) lost to follow up.

- Seventy five patients (36%) are being followed with functioning graft

Patient survival rates at one, five, and ten years were 96, 87.8 and 84%, respectively (Fig. 6).

Graft survival rates at one, five, and ten years were 87, 70.4 and 63.9%, respectively (Fig. 7).

Summery of the Post transplantation outcome in both groups;

In summery; the post transplantation outcome in patients (group I) were compared with patient (group II) in the same period of time but in different countries.

	Group I (n = 138)	Group II (n = 230)	P value
Recipient age (years)	45.4 ± 13.8	42 ± 12	
Mean ± SD			
Range	18-65	18-55	
Recipient sex (M/F)	(78/60) 1.3:1	(147/83) 1.7:1	

Table 3. Recipient's age and sex distribution in both groups.

	Group I(n = 138)	Group II (n = 230)	P value
Acute rejection episode	(10) 7.2%	(34) 14.8%	0.038
Chronic rejection	(32) 23%	(47) 20.4%	
Resume dialysis	(3) 2.3%	(26) 12.3%	0.001
Death	(7) 6.0%	(37) 16%	0.001
UTI	(27) 26.8%	(60) 26%	
Infectious complications (overall)	5%	25%	
HCV	(0) 0%	(30) 12.6%	
HBV	(0) 0%	(15) 6.0%	
CMV	(11) 4.3%	(11) 4.8%	
DM	(1) 0.7%	(48) 2.9%	0.001
Hypertension	(13) 9.4%	(153) 66.5%	0.001
Malignancy (KS)	(0) 0%	(4) 1.7%	
Urological complications	(7) 5%	(12) 5%	
Surgical complications	(9) 6.5%	(20) 8.6%	0.002

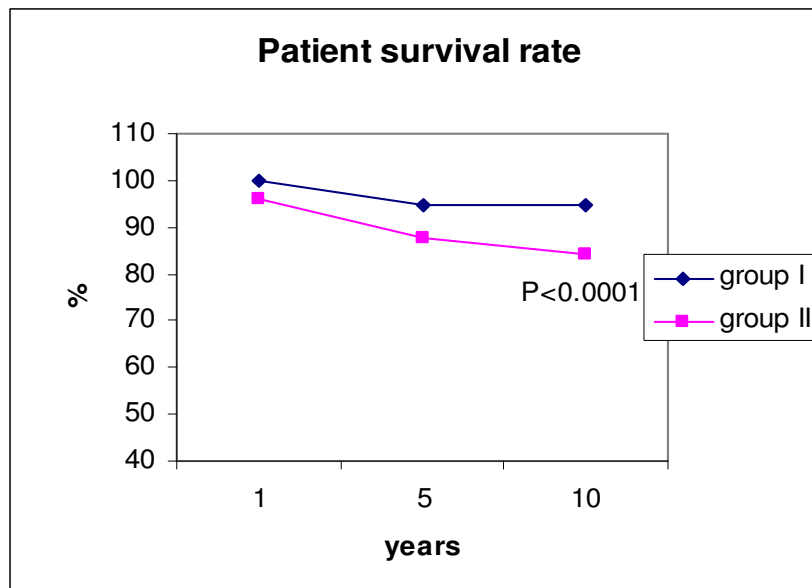
Table 4. Medical, infectious and surgical complications.

Results

The patient survival rates at one, five, and ten years in patients (group I) were compared with patient (group II) in the same period of time (Table 5).

	Group I(n = 138)	Group II (n = 230)	P value
One year	100%	96%	
Five years	94.9%	87.8%	0.001
Ten years	94.2%	83.9%	<0.0001

Table 5. Patient survival rate in both groups.



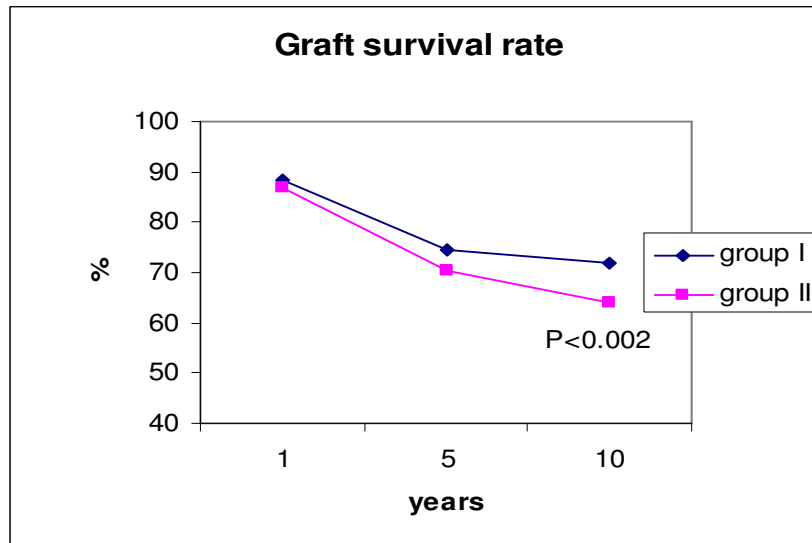
(Fig. 6) Patient's survival rate in both groups.

Results

The Graft survival rates at one, five, and ten years in patients (group I) were compared with patient (group II) in the same period of time (Table 6).

	Group I(n = 138)	Group II (n = 230)	P value
One year	88.5%	87%	
Five years	74.6%	70.4%	
Ten years	71.7%	63.9%	<0.002

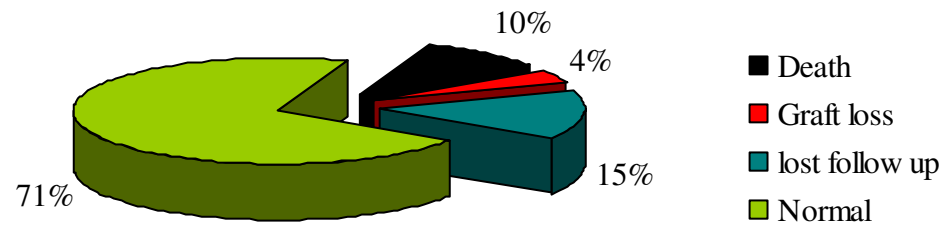
Table 6. Graft survival rate in both groups.



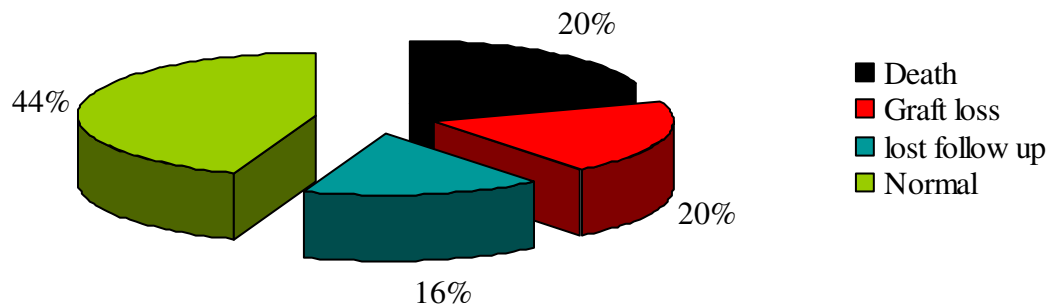
(Fig. 7) Graft survival rate in both groups.

Results

The over all ten years post transplantation follow up in patients (group I) were compared with patient (group II) in the same period of time but in different countries.



(Fig.4) Patients and Graft outcome in Group I.



(Fig. 5) Patients and Graft outcome in Group II.

DISCUSSION

Renal transplantation offers patients with end stage renal disease the best opportunity for rehabilitation and long term survival [109]. However, there is a critical shortage of transplantable kidneys worldwide.

In Libya, with around six million populations, although, living as well as cadaveric donations are permitted [130], the living related kidney transplant program was started on 1989 until 1996, during that period only 64 patients were transplanted, and then the program faced some difficulties where it was stopped [64] to be resumed again in 2004 and till 2005 further 50 patients were transplanted, that means living related donation is too much low. On the other hand, till now there is no cadaver transplantation program, its out of religious or political origin, its only due to lack of public understandings, therefore, the choice for that patient who have no compatible related donor is either to stay on dialysis therapy which is totally provided and supported by the Government or to go abroad of their own accord to countries where commercial kidney transplantation is available like India, Pakistan, Egypt and Iraq, where they bought kidneys for US \$ 1000-10,000. Hence, the total cost of the transplant (all included) was far less than that in the western countries.

The tendency to go abroad to India continued until it was abandoned due to the Indian legislation prohibiting live unrelated donor transplants for foreigners in 1994, leading to shift of patients to Pakistan and Iraq. There were reports suggesting that wealthy recipients from the Middle East who had gone to India or other countries in the third world for LNRD transplants had received inferior medical care, had sustained higher than normal complication rates, and had been financially exploited along with their donors [16]. More recently, though, there is a shift to LNRD in countries with more stringent ethical laws. The United States Renal Data records show that transplant centers in the country reported a ten fold increase in LNRD compared to only 16% and 68% increase in cadaver and LRD respectively.

Patients who returned back to Libya, most of them came to renal unit at Zahra kidney centre (the place of this study) for follow up. Preoperatively, these patients were not carefully selected and prepared and the criteria of suitability for transplantation were not strict, they are not properly instructed

About their treatment, also they did not get adequate pre transplant education and not informed of possible complications including rejection and graft loss. Most of the patients did not meet their donors. The mean duration from their travel till they got transplant and return back to Libya, was between 2 and 3 weeks, which is very short time for pre operative preparation for both the recipients and their donors, the same observations have been reported by other Authors [18]. Their experience has negative feelings toward the standard of hospital hygiene; hence they were exposed to serious infections. Furthermore, most of the patients were not given medical reports, there were little or no information was given to doctors who following them. These results substantiate the impression that commercial transplantation does not conform to the high standards of renal transplant medicine [16, 94 and 106].

Commercial transplantation is not only controversial for ethical aspects, but it has been reported to result in serious complications in the postoperative period that cause high rates of morbidity and mortality and it also carries the risk of a negative effect on local transplant programs. However, despite these arguments, unethical transplantation is an ongoing therapy and transplant physicians are frequently faced the problem of treating complications of this type of transplantation.

Without going into the ethical debate, it may be worthwhile examining the results of paid unrelated donor transplants carried out in the developing countries and compare these with unrelated donor transplants from the industrialized countries as well as with transplants performed without the involvement of commercial transaction in the same center.

In this study, we compared the long term outcome of commercial kidney transplant patients with patients who were transplanted in Uni-klinik Düsseldorf during the same period of time. The results show that the recipients were mainly males in their middle age in both groups.

Acute Rejection; is the most common cause of kidney malfunctioning or failure in the early post transplantation [66].

There is evidence that acute rejection can influence the long term outcome of renal transplantation [46], i.e. Graft half life is longer in patients who never experienced acute rejection. However, long term graft survival is better in

Patients who had only a single episode than in patients with two or more episodes of rejection. Moreover, Opelz et al [83] showed that when rejection is completely reversible, it does not affect 5 year graft survival.

Sijpkens et al [114] pointed out that the prognosis is worse for patients who had late rejection than for those who had early rejection: 10 year graft survival censored by death was 86% for patients who developed rejection by the third post transplant month and 45% for patients who had rejection after the third month. On the other hand, long term graft survival is usually excellent in patients with borderline or grade I rejection, according to the Banff '97 classification, while the prognosis is worse for patients with grade II and very poor for patients with grade III rejection.

In our study, Acute rejection episode observed more in the study group (group II) (14.8%), compared with group I (7.2%), which is a statistically significant ($p=0.038$), that is probably due to the careless selected and unprepared transplantations (Table 4).

Chronic allograft nephropathy; is the most common cause of late graft dysfunction due to a progressive and irreversible histological and functional deterioration of the transplanted kidney. The main cause of late graft failure is chronic rejection and chronic toxicity of calcineurin inhibitors.

In this study, although, chronic rejection was almost all equal in both groups, the patients who had commercial transplantation had resumed dialysis in the first two years post operatively (12.3%), compared with patients in group I (2.8%) ($P=0.001$) which is highly significant (Table 4).

Infectious complications; Aggressive immunosuppression may reactivate latent viruses, which usually causes graft failure. Hence, it may enhance the development of 'de novo' glomerulonephritis. The most frequent forms are membranous nephropathy usually related to HBV infection and membranoproliferative glomerulonephritis in HCV carriers [92].

CMV infection is a frequent complication in renal transplantation. The infection can increase the risk of acute and chronic rejection through overproduction of mediators, cytokines, chemokines and growth factors. There were more infectious complications like; pneumonia, pulmonary Tuberculosis and wound infection, among patients who had commercial transplantation (group II), compared with patients in group I.

The over all infectious complications percentage in group II and group I are (25.9 % vs. 5%) respectively, which are statistically significant (Table 4).

The presence of urinary tract infection during the post operative course is common in both groups and has no statistical difference.

Patients who have HBsAg positive have less favorable outcome after transplantation [101], also post transplant hepatic diseases associated with increased morbidity and mortality [101].

There was no case of hepatitis B or C viruses have been reported among patients group I. While Hepatitis infections found in high rates among patient's group II, some of them were complicated with chronic active hepatitis and liver cirrhosis.

Malignancy: occurrence of immunosuppression related malignancy is greatest in patients receiving several courses of high doses of intensive immunosuppressive therapy.

Kaposi sarcoma (KS), is one of the common post transplant malignancy, it accounts for 34% of the malignancies associated with immunosuppressant for renal transplantation, three to six months after transplantation.

In this study, 4 cases (1.7%) with Kaposi sarcoma was reported in patients group II, which is mainly due to over immunosuppression [65]. Or as a result of viral infection with human herpes virus 8 (HHV-8) [116].

Hypertension; long term patients and their grafts survival may be negatively influenced by post transplant hypertension [29]. It is often drug induced during post transplantation. Opelz et al [84] showed a strong association between the values of blood pressure and the risk of chronic graft dysfunction. The presence of post transplant hypertension in our patients is so high among group II (66.5%) compared with patients group I (9.4%) ($p=0.001$) (Table 4).

Post transplant Diabetes Mellitus; Steroids and Tacrolimus are well recognized to induce diabetes. 20-25% [57] of renal transplant recipients develop overt “de novo” diabetes. These patients have an increased risk of cardiac, cerebrovascular and peripheral vascular disease.

Moreover, patients with post transplant diabetes may develop a diabetic nephropathy and graft dysfunction in the long term [57]. The development of post transplant diabetes, in our study occurred in (0.7% and 2.9%) in group I and group II, respectively ($P=0.001$) (Table 4).

Surgical complications; may have a profound negative effect on the allograft survival and on patient survival as well [50]. Obviously, prevention of these complications is the best remedy. A clear understanding of the causes of complications and prompt diagnosis and treatment are the corner stones of a successful outcome and minimizing the impact on graft and patient survival.

We found the initial surgical complications like; wound infection in 5 cases (2%), two patients had opened wound with abscess formation, in group II.

Poor anastomosis or if a plaque is present in the recipient vessel can lead to allograft artery stenosis in 1-2% of post transplant patients.

Our data observed, a trend towards more graft artery stenosis in patients group I (living related donor transplantation), as it occurred in 12 cases (8.7%). One third was due to vascular complications caused by severe atherosclerosis of the recipients, despite their young age. The other complications were observed in patients, who received kidneys with vascular abnormalities such as fibromuscular dysplasia or multiple arteries, fortunately, it was saved after an early diagnosis of perfusion problems. As we know that, vascular abnormalities do not necessarily represent a contraindication for donation, but donor and recipient must obtain sufficient information about the increased probability of complication and the graft must be followed and managed thoroughly [123].

Urinary fistula and stricture took place in only 7 cases (5%) in patient's group I, while it developed in 12 cases (5%) in patient's group II. Without significance.

Patients group II reported to be complicated by lymphocele formation in 20 cases (9%) in the first months post operatively, while we have found 9 cases (6.5%) in patient's group I.

Renal function, including measurements of glomerular filtration rate and serum creatinine levels have become more important as outcome measures.

The outcome measures of transplantation are largely dependent on a number of factors;

Before transplantation factors include; the donor (living v/s cadaver, age and HLA system) [88], as well as the recipient (age, immunological reactivity, potential sensitization and duration of dialysis). It has been fully accepted one is kidney origin, i.e. living donor surviving longer than cadaver [29].

Further advantages of living donor kidney transplantation are; no brain death injury, no preservation or ischemic injuries. Also there is evidence that long term survival is better for transplants with no antigen mismatch than for mismatched transplants, lesser degrees of mismatch are of minor clinical relevance. For these reasons, the preparation and follow up of the recipient requires a great amount of precaution.

After transplantation a number of events may put graft function at risk like; delayed graft function, acute and chronic immunological and non immunological graft damages [88], potential recurrence of the primary renal disease in the allograft, de novo renal disease triggered by infections, drugs or autoimmunity and non specific progression promoters, such as diabetes, hypertension, proteinuria, nephrotoxic agents and/or viral infections.

The duration of dialysis treatment has a great influence on the outcome. Hence, there is a strong evidence suggests that the results of pre emptive transplantation are far better. Meier-Kriesche and Kaplan et al [75] demonstrated that the longer the time on dialysis, the worse the long term outcome of renal transplantation. Recently published data from the US Registry could point out the importance of a short waiting time. In patients with less than 6 months on dialysis, the 10 year graft survival was 63% but was only 29% in patients with a waiting time of more than 24 months. These impressive data are an argument for pre emptive living donor kidney transplantation.

Also, there is close relationship between early onset of urine output and improved outcome on each subsequent level, and every effort should be made to institute early urine output. Immediate onset of urine production and large urine volumes are more beneficial than oliguria or no urine at all.

The adequate renal function is physiologically more meaningful than just large urine volumes. Some renal function, even though not optimal but enough to avoid dialysis is preferable to delayed function necessitating haemodialysis in the early post operative phase. Delayed function offers a better prognosis for the patient than does never functioning kidney, or graft loss, which is the worst scenario of the kidney transplant procedure.

On the other hand, the occurrence of delayed graft function may require dialysis, may prolong hospitalization and may expose to an increased risk of infection. However, there is agreement that the combination of delayed graft function with rejection has a deleterious effect on the graft survival [92].

The potential development of chronic graft dysfunction is from the most frequent causes, which are either; chronic rejection (often triggered by preceding acute rejection, delayed graft function or poor compliance), or calcineurin inhibitors nephrotoxicity (more likely to develop in kidneys from elderly or marginal donors) [88].

These are the main factors that affect the outcome of the transplant, particularly in the long term.

Patient and graft survival outcome data were meaningful variables when survival percentages were in the 50-60% range. Currently, survival rates exceed 95% for patient and 90% for graft survival at one year. Therefore, these variables are less practical from a statistical standpoint to demonstrate improvement with a new treatment, i.e. an immunosuppressive drug. The incidence of rejection has also decreased in some centres to 20% or less within one year, making rejection a less practical method of measuring the outcome of transplantation.

During the last two decades, a significant progress has been achieved in the graft and patient survival rates after renal transplantation. Although numerous studies on five and ten years survival of kidney grafts and their recipients have been published, data at 15 years or more are rare [29].

In our data, although, the overall one year recipient survival rate in group I was 100%, compared to 96% for the commercial transplantation recipients, which is not statistically significant.

The patient survival rates were different in the five and ten years between the two groups (87.8% and 84%), respectively for group II and (94.9% and 94.2%), respectively for group I which is highly significant ($P < 0.0001$).

The 10 year actuarial graft survival achieves 71.7 % for kidneys of related living donor. This was statistically comparable to the results obtained from patients with bought grafts (Commercial) which showed a lower survive (63.9%) ($P < 0.002$) (Fig. 7), while it was not statistically significant in the first and five years post transplantation.

Generally speaking, the major causes of renal transplant patient loss are death from cardio vascular, malignant or infectious disease, and loss of the allograft from chronic renal dysfunction associated with the development of graft fibrosis and glomerulosclerosis [15 and 88].

Death is the main cause of failure of a functioning graft especially in old patients [88], since death at advanced age is due mainly to cardiovascular disease, infectious complications and malignancy [92]. On the other hand, the risk of graft failure caused by acute or chronic rejection tends to decrease with age.

Collectively, the outcome during ten years follows up period after transplantation of our patients is as follows:

In group I; seven patients (6%) died from which 4 patients (57%) died with functioning grafts. Out of these, 6 patients were died shortly after transplantation (during the first two year). The main causes of death were; cardiovascular complications in 2 cases (28.5%) and graft failure in 2 cases (28.5%).

Three patients (2.3%) lost their grafts and resumed dialysis as a replacement therapy, 60 patients (43.4%) are being still follow up with functioning grafts and only 10 patients (9%) were lost to follow up.

While in group II; thirty seven patients (16%) of the total patients were died, out of them 8 patients (21.6%) died with functioning grafts, 25 patients (53%) died in the first two years post transplantation, which reflects a high mortality in the early post operative period, mainly due to the high rate of complication like infections, rejections, surgical and medical complications. The patients who died had multiple complications, like; infections 14 (30%),

Cardiovascular complications 9 (24%), and graft failure 9 (24%), where they were the commonest known causes of death.

Seventy five patients (36%) still have functioning grafts and are being still follow up, 86 patients (38%) lost their grafts and resumed dialysis and 30 patients (13%) were lost to follow up.

We conclude that the major risk factors for graft failure like graft rejections, infectious complications, development of post transplant diabetes and hypertension are seen more in patients group II that explain their poor long term outcome and their grafts.

There is an interaction between the medical and ethical aspects when we discussing the issue of commercial transplantation. From medical point of view, it is well established that living non related transplantation had better graft and patient survival rates than cadaveric [29], and are comparable with those of living related donor transplantations [1 and 123]. However, the same considerations cannot be applied to (commercial) transplantation, since in many series the results are not as favourable, due to surgical and medical problems.

Many published literatures (Table 7) suggested that the outcome of commercial transplants is inferior to those that are carried out under careful medical care. A high rate of transmission of infections including HIV, fungi and hepatitis viruses, as well as high mortality rates.

During the period between 1996 and 1997 when I was working at the out patient clinic at Zahra kidney centre, I had noticed and reported on around 70 patients had got commercial kidney transplantation at Iraq, they came with variable kinds of early post operative complications [63].

Chugh et al [16] the medical as well as the surgical complications following commercial transplantations in developing countries have been described as the major cause of morbidity and mortality for both the patients and the donors. Although the reason for these complications is obscure, very probably it is due to surgical methods that do not meet the current standards of transplantation. In addition to the medical problems, it has been apprehended that commercial transplants would hinder the growth of cadaver transplant programs.

Salahuden et al [106] reported on 1 year mortality among group of 130 patients from United Arab Emirates and Oman who underwent commercial transplants in India. About 64% of the deaths took place within the first 3 months. The major cause of death was infection. They speculated that some of these infections could have been transmitted through contaminated allograft and or blood products used in the preoperative period. In addition. Some of patients had positive HBsAg after transplantation. The 1 year patient survival among living related donor transplants at their own centre during that time was 98%.

Several other workers reported similar results amongst commercial transplants performed in many countries including India, Iraq, Macedonia and Estonia [26].

Al Asfari et al [4] from Syria reported that 29% of early mortality among their cohort of 38 commercial recipients. Rejection and infections were the most common causes of death. In their experience both recipients and donors had gone through minimal pre-transplant evaluation.

Hussein et al [49] noted 52 infection episodes in 56 patients including HIV in 9% of cases. In addition, over 30% of patients experienced urological complications including; urinary leaks, ureteral obstruction, catheter related infections, lymphocele and vascular thrombosis. The patients were on inappropriately high doses of Cyclosporine A reflected by very high blood levels of the drug. In general, commercial recipients required much more follow up care than patients who received living related donor transplants locally.

Colakoglu et al [18] has studied 127 Turkish patients who went to India for commercial renal transplantations. These patients had surgical problems, infections, acute rejection, cyclosporine nephrotoxicity and hepatic problems. The authors suspected that the true mortality and graft loss were likely to be higher than reported, and most of these complications can be prevented by adequate preoperative management.

Berkman et al [11] noted a higher incidence of *Pneumocystis Carinii* pneumonia among patients returning to their country after receiving commercial transplants in Iraq or India. None of the patients had received Cotrimoxazole prophylaxis, which is a routine practice in the Western countries.

Non infectious medical complications including congestive cardiac failure, post transplant diabetes mellitus leading to diabetic ketoacidosis and acute myocardial infarction, were also reported among these recipients. No attempt is even made to perform HLA matched transplants.

Sever et al [110] reported on 115 patients who had been commercially transplanted in various countries had complicated post transplant period by numerous surgical, medical complications, and infections like; malaria, invasive fungal infections, and pneumonia due to various opportunistic pathogens. Graft survival rates were worse than conventional living related transplantations at the midterm.

Daul et al [22] reported on 2 German patients who died in the first month post commercial transplantation after coming back from India due to severe infections, also he had write on the complications followed the commercial renal transplantation in the third world like; fungal and viral infections (hepatitis B, C, HIV and CMV) due to poorly prepared preoperative examinations, uncontrolled high immunosuppressive doses and the lake of the hygienic standard of the surgical technique.

Devol et al [25] reported on 540 patients from multi Saudian centres, which had been commercially transplanted in India, they complicated with infections like; hepatitis and HIV.

Mansy et al [69] reported on 12 patients from Saudi Arabia who had been commercially transplanted, they had low two years patient survival rate.

Morad et al [76] reported on 515 Malaysian patients who had been commercially transplanted and complicated by hepatitis.

Onwubalili et al [82] reported on 16 patients with infections like; hepatitis and HIV. Also the patient survival rates were worse at the 5 years.

Ivanovski et al [52] reported on 14 Macedonian patients who had been commercially transplanted in India they had low patient survival rate.

Frishberg et al [39] observed a high incidence of post transplant urological complications in 18 children who have got commercial transplantation in Iraq.

Jacobs et al [53] from USA reported also on a high incidence of post transplant surgical complications.

Higgins et al [47] reported on 9 patients in the UK who had been commercially transplanted in China, India and Pakistan they were complicated post operative by numerous infections like; hepatitis C and B. and even more the use of modern immunosuppressions did not appear to be protective against poor practice.

Kennedy et al [59] recently, wrote on hepatitis and other viral infections and lower survival rates among Australian patients who under went commercial renal transplantations in China and India.

Friedlaender et al [37 and 38], reported on 79 patients, they had low one year patient as well as graft survival rate, and 10% mortality at one year.

These reports are not representative of the outcome of all such transplants. However, this represents only a few of thousands that have been performed. Indeed, these results has not compared to the results of non-related transplants done in the west [121].

Kidney transplantation from living related donation and living non related donors i.e. between persons who have close emotional bonds only, has been performed for many years with good results. The emotionally related kidney donation excludes by definition all living unrelated donations with kidneys purchased from strangers [12].

In the following decades, transplantations with organs from living related donations have been performed with good results, showed better graft function than cadaveric grafts [12], especially in USA and Scandinavia, since the mid 1980s an increasing number of living unrelated donors are being accepted worldwide. In 2002 the number of living kidney transplantations in the US surpassed for the first time the number of cadaver kidney transplantation. Surprisingly, the three years graft survival of kidneys from living unrelated donor was not significantly different from that of HLA identical siblings or other living related donor transplantations.

In US in particular, also in other countries, although, kidney transplantation from living non related donor was described as early as the mid 1980s with

Good short term and long term results and low short term and long term risks for the donors, it remains an underutilized resource, despite their high graft survival rates.

In Düsseldorf centre they always considered transplantation either between related or unrelated persons only under circumstances, where emotional relation and high motivation were evident and other purposes could be excluded. A further key point during workup was to exclude even small additional risks for the donor. Therefore, the evaluation procedure consists of multiple discussions between donors and recipients and the medical and surgical team as well as with the psychologist [123].

Discussion

Table 7. Summary of some published literatures reported on the outcome of commercial transplants performed in different centres:

Author	Date of study	Country of study	Place of transplant	No. of cases	Patient Survival Rate	Post transplant compl.
Salahuden [106]	1990	Oman	India	131	81%(1y)	HIV, TB hepatitis
Onwubali [82]	1994	Saudi Arabia	India	16	75%(5y)	HIV, HBV, HCV
Al Asfari [4]	1995	Syria	India, Iraq	38	Not reported	Early mortality
Mansy [69]	1996	Saudi Arabia	India	12	70%(2y)	Not reported
Hussein [49]	1996	Saudi Arabian	India	56	Not reported	HIV
Daul [22]	1996	Germany	India	2	Not reported	Early mortality & infections
Devol [25]	1997	Saudi Arabian	India	540	95%(1y)	HIV, HBV
Berkman [11]	1997	Israel	India, Iraq	270	Not reported	PCP *
Lahresh [63]	1997	Libya	Iraq	70	Not reported	Surgical compli.
Ivanovski [52]	1997	Macedon	India	14	78%	Not reported
Frishberg [39]	1998	Israel	Iraq	18	94%(1y)	Surgical compli.
Colakoglu [18]	1998	Turkey	India	127	81%(1y)	Surgical compli. & infections
Morad [76]	2000	Malaysia	Not reported	515	92%(1y)	HBV
Sever [110]	2001	Turkey	India, Iraq, Iran	115	90%(1y)	malaria, HBV fungal infect.
Higgins [47]	2003	UK	India and Pakistan	9	Not reported	HBV & HCV
Jacobs [53]	2003	USA	Iraq	18	94%(1y)	Surgical compli.
Friedlaender [37&38]	2003	Israel	Iraq	79	89%(1y)	Early mortality
Kennedy [59]	2005	Australia	China and India	16	80%(1y)	HBV, CMV
Total number				2046		

* PCP = pneumocystis carinii pneumonia.

CONCLUSION

Renal transplantation offers patients with end stage renal disease the best opportunity for rehabilitation and long term survival. However, the major factor limiting transplantation rates is availability of donor kidneys. The lack of transplantable organs is a universal problem, especially in developing countries; this has led to the growth of commercial programs in renal transplantation.

The main centres for these practices were initially in India, more recently, programs have developed in Iraq, Iran, Eastern Europe, South America, South Africa, China and the Philippines.

The lack of available kidneys for donation in Libya has led most of the patients with end stage kidney disease to go abroad where organs are more available because donors are financially compensated for their kidneys.

We have investigated a total number of 230 Libyan patients who had commercial transplantation in some of the third world countries and they been followed up at Zahra kidney centre in Libya, and we do compared them with a total number of 138 patients who had living related donor transplantation at Uni-klinik Düsseldorf in Germany, in the same period of time, between 1994 and 2004, with comparable age, sex ratio and original kidney diseases.

We had reviewed many articles in the literatures that reported on the possible complications and outcome of overseas commercial kidney transplantations, in the period from 1990 till 2005, with more than 2000 reported cases and we found that they are comparable with our results.

There was lack of communication between the transplant team who they did these operations and the units caring these patients in Libya. Our experience is similar to that reported by others.

Our study covers a period of 10 years follow up, highlights on some areas of concern about commercial kidney transplantation, like; Infectious complications, medical and surgical complications and short and long term outcome of the patients as well as their grafts.

It showed that, the 10 year graft survival rate was lower in patients with commercial transplantation than in those who had living related donor transplantation in Germany.

We could conclude that commercial transplantation carries high rate of medical complications like, graft rejection and infectious complications due to careless prepared operations. Also has high rate of malignancy like Kaposi sarcoma due to excessive immunosuppressions. Moreover, surgical complications like, wound infections and lymphocele due to mishandled and badly performed operations.

Infections like; hepatitis B and C among patients who had commercial transplantation are very high, either from an infected donor organ or blood products as a result of inadequate pre operative workup. The screening procedures of those who had commercial transplant programs are not evident, despite a generally high incidence of these infections in the populations of the countries performing commercial transplantation, fortunately, HIV was not reported in our patients.

The major causes of death are from cardiovascular, infectious diseases and loss of the allograft from chronic graft dysfunction.

The high mortality rate as well as morbidity in the first two years after transplantation among these patients reflected by the high rate of complications like rejections, infections, medical and surgical complications.

Patients and graft loss were remarkable in patients who had commercial renal transplantation in the early post operative period, instead of improving their life quality and expectancy in comparison with those who had living related renal transplantation in Germany.

Organ donation had been approved as it provides a hope for those patients who suffering an end stage organ failure, provided that it should be free of commercialism, on the other hand, commercial transplantations, beside it's complications, from medical point of view, it has been rejected by all charities, religions, societies and laws, and it considered being unethical practice.

Kidney transplantation from living non related donors was performed with a lower HLA match, the results are equivalent to living related donor transplantation. Also the recipient and the graft outcome were superior to cadaver kidney transplantation. Therefore, it represents a valuable option for patients with end stage renal disease and should be allowed provided that they are carefully selected and performed.

Finally, we concluded that, the long term outcome of commercial transplantation is inferior to that of living related or un related renal transplantation and in order to solve the problem of organ shortage for donation, a new prospective in living donor transplantation like; altruistic donation, cross over or exchange donor programs. Since, it is an ethically accepted practice; it could be used to alleviate the organ shortage for patients who do not have proper living related donor.

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Glossary

ALG	Anti Lymphocyte Globulin
APC	Antigen Presenting Cells
AZA	Azathioprine
CAN	Chronic Allograft Nephropathy
CGN	Chronic Glomerulonephritis
CMV	Cytomegalovirus
CsA	Cyclosporine A
DM	Diabetes Mellitus
EBV	Epstein Barr Virus
ESKD	End Stage Kidney Disease
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HHV	Human Herpes Virus
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HTN	Hypertension
HUS	Haemolytic uraemic Syndrom
IF	Interferon
IL	Interleukin
i.v.	intra venous
KS	Kaposi Sarcoma
LNRD	Living Non Related Donor
LRD	Living Related Donor
mAb	monoclonal Antibody
MHC	Major Histocompatibility Complex
MMF	Mycophenolate Mofetil
OKT3	murmonab CD3
OPTN	Organ Procurement and Transplant Network
PCP	Pneumocystis Carinii Pneumonia
p.o.	per os
PRA	Panel Reactive Antibody
PVN	Polyoma Virus Nephropathy
SD	Standard Deviation
SLE	systemic Lupus Erythematosus
TGF	Transforming Growth Factor
TNF	Tumor Necrosis Factor
UNOS	United Network for Organ Sharing

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- Experience in living related kidney transplantation in Libya. 6th ASNRT congress, 2000, Marrokko.
- Ulcerative colitis post renal transplantation; case report. 7th ASNRT congress, 2002, Bahrain.
- Infectious disease prevalence in Zawia area (Libya). 5th congress of the Libyan medical sciences, 2002, Libya.
- Long term outcome of the commercial renal transplantation. 35th congress of nephrology, 2005, Germany.
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Abstract

Long term post transplantation Outcome; Comparative Study between Emotionally Motivated and Commercial Renal Transplantation in two different centres.

Introduction: Kidney transplantation is to relieve patients of the burden of dialysis and to allow returning to productive life. However obtaining organs remains the major problem all over the world. This had led to development of new alternatives like; commercial transplantation in some countries, although it had been considered unethical, it has a high complications rate as well.

Aim: To compare the long term course and outcome of patients with commercial transplantations and living related kidney transplantation in two different centres.

Patients and Methods: A 368 kidney transplanted patients were examined retrospectively and classified into;

Group I: 138 patients had living kidney transplantation at Uni-klinik Düsseldorf in Germany.

Group II: 230 patients had commercial transplantation in some countries and followed up at Zahra kidney centre in Libya. Follow up data regarding medical, surgical complications, patient and graft survivals at one, five and ten years were reported.

Results: We compared group II group I, during the same period of time. The result showed; Acute rejection episode (14.8%) in (group II) and (7.2%) in (group I) ($p < 0.038$), Chronic rejection was equal in both groups, 12.3% had resumed dialysis in the first two years post operatively in (group II) compared group I (2.8%) ($P < 0.000$). Post transplant hypertension among group II (66.5%) compared with group I (9.4%) ($p = 0.001$) and post transplant diabetes, (0.7% and 2.9%) in group I and group II, respectively ($P = 0.001$). There were more infectious complications like hepatitis C and B, CMV, herpes zoster and Tuberculosis in group II (25.9 % vs. 5%), Surgical complications like graft artery Stenosis in living related donor transplantation (8.9 vs. 1%), Kaposi sarcoma in (in group II) 1.7% vs. 0). Patient survival rates were different in the five and ten years (87.8 and 84%, respectively for the group II and 94.2 and 94.2%, respectively for group I ($P = 0.0001$), 10-year graft survival was (71.7 %) for group I and (63.9%) for group II. ($P = 0.002$). Death in the (group I) was (6%). The main causes of death were; cardiovascular complications 2(28.5%) and graft failure 2(28.5%). While in group II; was (16%), the commonest causes of death; infection (30%), cardiovascular (24%), and graft failure 9 (24%).

Conclusions: The Outcome of commercial transplantation are inferior to Living related transplantation, because it carries a high rate of complications like; infections which are the major causes of morbidity and mortality and despite that the patient survival rate is comparable, graft survival is worse than conventional living related transplantations at the long term follow up.

